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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Aberg et al.

Application No.: 09/447,218 Art Unit: 1623

Filed: November 23, 1999 Examiner: Lawrence E. Crane

For: METHODS FOR TREATING URTICARIA USING DESCARBOETHOXYLORATADINE

Attorney Docket No.: 4821-362 (JD 208423-999361)

SUBMISSION OF EXHIBITS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to their Response filed January 9, 2006, Applicants note that the Response may have been filed without the Exhibits referred to therein. Accordingly, the Exhibits to the Response are submitted herewith.

No fee is believed to be due for the submission of this paper and the Exhibits. If any fees are required, however, please charge such fees to Jones Day Deposit Account No. 503013. A copy of this sheet is enclosed.

Respectfully Submitted,

Date: January 11, 2006

L0209

Hoon Choi (Limited Recog. No.)
Jones Day
51 Louisiana Avenue, N.W.
Washington, DC 20001-2113
(202) 879-3939

For: Anthony M. Insogna (Reg. No. 35,203)
Jones Day
12750 High Bluff Drive, Suite 300
San Diego, CA 92130
(858) 314-1200

Enclosure

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EXHIBIT 1

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09/527,844	03/17/2000	Timothy J. Barberich	4821-334-999	3697

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JONES DAY
51 Louisiana Aveue, N.W
WASHINGTON, DC 20001-2113

EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

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The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte TIMOTHY J. BARBERICH,
PAUL D. RUBIN and WILLIAM E. YELLE

MAILED
AUG 26 2005
U.S. PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

Appeal No. 2005-0906
Application No. 09/527,844

HEARD: July 12, 2005

Before MILLS, GRIMES, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-15 and 50-53. Claims 1 and 5 are representative of the subject matter on appeal, and read as follows:

1. A method of treating or prophylaxis of a disorder ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors in a patient which comprises administering to a patient in need of such treatment or prophylaxis a therapeutically effective amount of a ziprasidone metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

5. The method of claim 1 wherein the ziprasidone metabolite is ziprasidone sulfoxide or ziprasidone sulfone.

The examiner relies upon the following references:

Lowe, III et al. (Lowe)	4,831,031	May 16, 1989
Allen et al. (Allen)	5,312,925	May 17, 1994

Davis et al. (Davis), "Ziprasidone," CAPlus Abstract, Copyright 2002, American Chemical Society, referencing CNS Drugs, Vol. 8, No. 2, pp. 153-159 (1997).

Prakash et al. (Prakash), "Metabolism and Excretion of a new Antipsychotic Drug, Ziprasidone, in Humans," Drug Metabolism and Disposition, Vol. 25, No. 7, pp. 863-869 (1997).

Claims 1-4 and 6-9 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Davis. In addition, claims 1-15 and 50-53 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Davis, Lowe, Allen and Prakash. After careful review of the record and consideration of the issues before us, we reverse both rejections of record.

BACKGROUND

Ziprasidone is a highly potent 5-HT_2 and dopamine D_2 receptor antagonist, and while characterized as an antipsychotic, it may also have anxiolytic and antidepressant effects due to ability to inhibit serotonin and noradrenaline uptake. See Specification, page 1. According to the specification, at least twelve metabolites of ziprasidone have been identified in humans, but ~~that~~ the prior art has reported that the metabolites are not active at the D_2 and 5-HT_{2A} receptor sites. See id. at 1-2.

The specification teaches further that "Ziprasidone offers a number of benefits, but unfortunately many adverse effects are associated with its administration. Examples of adverse affects of ziprasidone include, but are not

limited to, nausea, somnolence, asthenia, dizziness, extra-pyramidal symptoms, akathisia, cardiovascular disturbances, male sexual dysfunction, and elevated serum liver enzyme levels. . . . It is thus desirable to find a compound which possesses advantages of ziprasidone but fewer of its disadvantages." Id. at 2-3.

Thus,

> [t]his invention relates to novel methods using, and compositions comprising, ziprasidone metabolites, preferably, ziprasidone sulfoxide and ziprasidone sulfone. These metabolites, prior to the present invention, have been reported to have little or no in vivo activity. The present invention encompasses the in vivo use of these metabolites, and their incorporation into pharmaceutical compositions and single unit dosage forms useful in the treatment and prevention of disorders that are ameliorated by the inhibition of serotonin reuptake at 5-HT_2 receptors and/or the inhibition of dopamine reuptake at dopamine D_2 receptors. Such disorders include psychotic and neuroleptic disorders. In a preferred embodiment, ziprasidone metabolites are used in the treatment or prevention of neuroleptic and related disorders in mammals, including humans.

Id. at 3.

The specification describes pharmaceutical compositions comprising ziprasidone metabolites, see id. at 7, as well as methods of preparing the sulfoxide and sulfone metabolites, see id. at 7-8.

DISCUSSION

The issues in this case turn primarily on claim construction—specifically the construction of the term "administering" in the claims.

According to the examiner, the term "administering" should be construed as encompassing the administration of the parent drug, ziprasidone, "because metabolites of ziprasidone are necessarily and inevitably formed under normal

condition[s] [sic] once ziprasidone is administered to a patient." Examiner's Answer, page 7.

Appellants argue that the examiner's construction of the term "administering" is contrary to its ordinary meaning. See Appeal Brief, page 10. Appellants argue that "administering" refers to "a compound that exists outside of the patient [which] is given, or applied to the patient." Id. Appellants argue further that the examiner's construction is contrary to unambiguous statements made during prosecution "that the term 'administration' or 'administering,' as used in the claims, means giving to a patient a compound as it exists outside of the body." Id. at 13.

During ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification as it would be interpreted by the ordinary artisan. See Phillips v. AWH Corp., 2005 WL 1620331, *9 (Fed. Cir.) (en banc) (citing In re Am. Acad. Of Sci. Tech. Ctr., 367 F.3d 1359, 1364 (Fed. Cir. 2004). Thus, it is "entirely appropriate . . . when conducting claim construction to rely heavily on the written description for guidance as to the meaning of the claims." Id.

In the case before us, the specification focuses entirely on the preparation of ziprasidone metabolites, teaching their synthesis and their incorporation into pharmaceutical compositions. Thus, we construe "administering" as used in the claims as requiring the ex vivo preparation of the ziprasidone metabolite, which

is then given to the patient, and excluding giving the patient the parent drug ziprasidone.

Claims 1-4 and 6-9 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Davis.[1]

According to the rejection:

> Davis [ ] discloses ziprasidone as an antipsychotic drug having high affinity for serotonin 5-Ht2 and dopamine D2 receptors. Davis [ ] also discloses administration of this drug to patients. Davis further indicates that clinical trials have shown ziprasidone to be effective in treating depression associated with schizophrenia and in reducing anxiety in patients about to undergo dental surgery.

Examiner's Answer, page 3.

It is axiomatic that in order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. See In re Schreiber, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed. Cir. 1997). As we have construed "administering" as requiring ex vivo preparation of the ziprasidone metabolite, which is then given to the patient, the Davis abstract does not anticipate the claim, as it does not

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[1] We note that the examiner relies solely on the abstract of the Davis article, and from our review of the record, it does not appear that the entire reference has been made of record. "Citation of and reliance upon an abstract is generally inappropriate where both the abstract and the underlying document are prior art." MPEP §706.02 (II) (8th edition, Revision 2, May 2004). Moreover, in order for meaningful appellate review to occur, the examiner must present a full and reasoned explanation of the rejection see, e.g., In re Lee, 277 F.3d 1338, 1342, 61 USPQ2d 1430, 1432 (Fed. Cir. 2002), and that would include analysis of the full underlying document.

teach or suggest the use of metabolites of ziprasidone in that manner. The rejection of claims 1-4 and 6-9 under 35 U.S.C. § 102(b) as being anticipated by Davis is thus reversed.

The examiner asserts that the administration of metabolites of ziprasidone is inherent in the administration of the parent drug, ziprasidone. See Examiner's Answer, page 6. The examiner cites Zenith Laboratories, Inc. v. Bristol Myers Squibb, Co., 19 F.3d 1418, 30 USPQ2d 1285 (Fed. Cir. 1994) in support of that assertion, arguing that case "provides that ziprasidone metabolites are necessarily and inevitably formed from the ziprasidone under normal condition[s] [sic]." Id.

We do not disagree that ziprasidone metabolites are "necessarily and inevitably formed" upon the administration of ziprasidone. Claim 1, however, as construed by the panel, requires the ex vivo preparation of the ziprasidone metabolite, which is then given to the patient. That limitation is neither taught nor suggested by the Davis abstract, and thus the Davis reference does not teach the method of claim 1. The court's decision in Zenith Laboratories is not on point, as the claim at issue in that case was drawn to a compound, and the court construed the claimed compound as not being limited to the compound in its preingested form. See id. 19 F.3d at 1422, 30 USPQ2d at 1288. Thus, the decision in that case, as in the case before us, turned on the construction of the claim, and we have construed the claim to exclude giving the patient the parent drug, ziprasidone.

The examiner argues further that instant claim 1 is analogous to a product-by-process claim, as "the product employed in a method claim[ ] may not be limited to the manipulations of the steps creating the product, only the structure implied by the steps, here, ziprasidone metabolites." Examiner's Answer, page 8. According to the examiner, as the patentability of a product does not depend on its method of production, it is irrelevant to the patentability of the claim whether the ziprasidone metabolite is synthesized ex vivo or produced through the metabolism of the parent drug. See Examiner's Answer, pages 8-9.

We do not find the examiner's reasoning to be persuasive. The claims at issue, such as claim 1, are not product-by-process claims. The claim as construed here requires the ex vivo preparation of the ziprasidone metabolite, which is then given to the patient, and as noted above, the Davis abstract does not teach or suggest giving a ziprasidone metabolite, which has been prepared ex vivo, to a patient.

We note that both the examiner and appellants argue that the holding in Schering Corp. v. Geneva Pharmaceuticals, Inc., 339 F.3d 1373, 67 USPQ2d 1664 (Fed. Cir. 2003) supports their position. In that case, the court held that claims drawn to a loratadine metabolite, DCL, were inherently anticipated by prior art drawn to the administration of loratadine, as "DCL necessarily and inevitably forms from loratadine under normal conditions." Id., 339 F.3d at 1378, 67 USPQ2d at 1668. That holding is distinguishable from the case before us

because the claims are not drawn to the metabolite per se, but to a method of administering the metabolite, which we have construed as requiring ex vivo preparation of the metabolite, which is then given to the patient.

In addition, appellants rely on the following language from Schering. See Appeal Brief, page 11.

> Finally, this court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs. With proper claiming, patent protection is available for metabolites of known drugs. . . .
>
> * * *
>
> A skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in *Kratz* and *Bergstrom*, or as a pharmaceutically composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The '233 patent would not provide an enabling disclosure to anticipate such claims because, for instance, the '233 patent does not disclose isolation of DCL.

Id., 339 F.3d at 1378, 67 USPQ2d at 1670.

We note that as we need not rely on the above passage from Schering in reaching our decision today, based on our construction of "administering," we decline to address the argument of whether the above passage is dictum, as argued by the examiner, or necessary to the holding in Schering, as argued by appellants.

Claims 1-15 and 50-53 stand rejected under 35 U.S.C. § 103(a) as being obvious over the combination of Davis, Lowe, Allen and Prakash.

Davis is relied upon as above. The examiner states that "Davis does not specifically teach metabolites of ziprasidone, the amounts (i.e., dosage), or routes of administration as instantly claimed." Examiner's Answer, page 4.

Lowe is relied upon for teaching that ziprasidone and ~~their~~ its pharmaceutically acceptable salts may be administered orally, in the form of tablets or capsules, or parentally. Allen is relied upon for teaching the use of ziprasidone hydrochloride as a neuroleptic agent. See id.

Prakash is cited for teaching the affinity of the sulfone and sulfoxide metabolites of ziprasidone for 5HT2 and D2 receptors. See id.

The rejection concludes:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to employ ziprasidone or any of its known salts or metabolites, including the sulfone and sulfoxides, in a method for treating neuroleptic disorders.
>
> One of ordinary skill in the art would have been motivated to employ ziprasidone or any of its known salts or metabolites in a method of treating neuroleptic disorders, because ziprasidone and ziprasidone hydrochloride are known in treating anxiety, depression associated with schizophrenia and situational anxiety (i.e. anxiety prior to dental surgery). Further, employment of different salts and metabolites of a known active, as an alternative form of different salts and metabolites of a known active, as an alternative form of drug delivery, is within the skill of the artisan and therefore obvious.

Id. at 4-5.

"[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to

combine the relevant teachings of the references.'" In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citation omitted). An adequate showing of motivation to combine requires "evidence that 'a skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.'" Ecolochem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1076 (Fed. Cir. 2000).

As argued by appellants, see Appeal Brief, page 16, Prakash teaches that "[t]he affinities of the sulfoxide and sulfone metabolites for 5-HT_2 and D_2 receptors are low with respect to ziprasidone, and are thus unlikely to contribute to its antipsychotic effects." Prakash, abstract. Thus, the skilled artisan would not have been motivated to substitute the sulfoxide and sulfone metabolites for the ziprasidone parent drug in the methods of Davis, Lowe and Allen. The examiner has therefore not established a prima facie case of obviousness, and the rejection of claims 1-15 and 50-53 under 35 U.S.C. § 103(a) is reversed.

The examiner argues that "Prakash teaches that sulfone or sulfoxide metabolites are major metabolites of ziprasidone . . . and that they possess agonistic affinities towards 5HT2 and D2 receptors. Such agonistic properties would have motivated the skilled artisan to employ sulfone or sulfoxide metabolites in a therapeutic regimen absent information to the contrary." Examiner's Answer, page 11. Moreover, according to the examiner, the fact that "sulfone or sulfoxide metabolites have low affinities towards their receptors is not

persuasive, because such [a] [sic] statement is not an indication that they are void of any value for the same therapeutic purpose as ziprasidone." Id. at 12.

The examiner's argument begs the issue, that is, whether a person of ordinary skill in the art would have been motivated to combine the references to arrive at the claimed invention. Obviousness is determined in view of the sum of all of the relevant teachings in the art, not isolated teachings in the art. See In re Kuderna, 426 F.2d 385, 389, 165 USPQ 575, 578 (CCPA 1970); see also In re Shuman, 361 F.2d 1008, 1012, 150 USPQ 54, 57 (CCPA 1966). In assessing the teachings of the prior art references, the examiner should also consider those disclosures that may teach away from the invention. See In re Geisler, 116 F.3d 1465, 1469, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997). As discussed above, Prakash, although arguably teaching that the sulfone and sulfoxide metabolites have some affinity for the 5-HT_2 and D_2 receptors, specifically teaches that the affinities are low as compared to ziprasidone, and are thus unlikely to contribute to its antipsychotic effects, and thus Prakash would not motivate the ordinary artisan to substitute ziprasidone metabolites for ziprasidone in the method taught by the other references.

CONCLUSION

Based on our construction of "administering" as used in the claims at issue, we reverse the rejection of claims 1-4 and 6-9 under 35 U.S.C. § 102(b) as being anticipated by Davis. Moreover, we also reverse the rejection of claims 1-15 and 50-53 under 35 U.S.C. § 103(a) as being obvious over the combination of Davis, Lowe, Allen and Prakash, as the examiner failed to set forth a prima facie case of obviousness.

REVERSED

Demetra J. Mills
Administrative Patent Judge)
)
)
)
) BOARD OF PATENT
)
Eric Grimes) APPEALS AND
Administrative Patent Judge)
)
) INTERFERENCES
)
Lora M. Green)
Administrative Patent Judge)

JONES DAY
51 LOUISIANA AVENUE, N.W.
WASHINGTON, D.C. 20001-2113

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EXHIBIT 2

Contact Dermatitis, 1997, 36, 147–149
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CONTACT DERMATITIS
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Skin reactions to hydroxyzine

M. MICHEL, A. DOMPMARTIN, S. LOUVET, C. SZCZURKO, B. CASTEL AND D. LEROY
Department of Dermatology of Caen, France

Sensitivity to histamine H1-antagonists has mainly been observed with phenothiazine and ethylenediamine, and is very rare with hydroxyzine. We report 3 cases of sensitization to hydroxyzine, which was prescribed to treat urticaria and atopic dermatitis. A generalized maculopapular eruption appeared shortly after taking the drug. Patch tests with Atarax® tablet were positive +++, and ++ or +++ with different dilutions of hydroxyzine. Patch tests with ethylenediamine, piperazine and other antihistamines were negative; therefore, there is no cross-allergy. We believe these rapid systemic reactions to hydroxyzine after the initial dose may have been due to prior systemic sensitivity to this drug, which cannot be used topically. Allergy to antihistamines must be considered when cutaneous lesions worsen on such therapy.

Key words: hydroxyzine; histamine H1-antagonists; antihistamine drug eruption; adverse drug reaction; lack of cross-sensitivity. © Munksgaard, 1997.

Accepted for publication 23 November 1996

Adverse drug reactions to histamine H1–antagonists are rare. This chemical family is divided into several groups ; phenothiazine and ethylenediamine subgroups are the main potential allergens (1). Allergy to hydroxyzine, which is close in structure to piperazine, has rarely been reported (2). We report 3 cases.

Patients and Methods

Patient no. 1

In December 1992, a 65–year-old woman was referred to our department with an adverse cutaneous drug reaction to Lariam® (mefloquine: Roche, Neuilly-Sur-Seine, France). To calm the pruritus, treatment with Atarax® tablets 100 mg/day (hydroxyzine: UCB Pharma, Nanterre, France) was introduced. At that time, we were surprised that, although Lariam® had been stopped the eruption healed so slowly. In January 1993, Atarax® was withdrawn. In April 1993, the patient developed urticaria which was treated with Atarax® 25 mg/day and Clarityne® tablets 10 mg/day. 12 h later, a generalised maculopapular eruption appeared. The eruption healed after discontinuance of Atarax® and Clarityne®. Urticaria was also cured. Patch testing was performed in January 1994 and June 1994.

Patient no. 2

For 20 years, a 36–year-old woman had eczema of the face and hands. She was atopic but she also had contact dermatitis from colophony, balsam of Peru, fragrance and oakmoss. Recurrences of eczema were treated with topical corticosteroids and several antihistamines, including Atarax®. In July 1995, she presented with an acute eczema of the face treated with Atarax® 25 mg/day and Noctran® (clorazepate dipotassique, acepromazine, aceprometazine: Menarini, Rungis, France). 3 days later, a generalized maculopapular eruption appeared. This eruption healed after discontinuation of Atarax® and Noctran®. Patch testing was performed in September 1995 and April 1996.

Patient no. 3

In December 1995, a 35–year-old woman was admitted at risk of premature labor. She was treated with Natisédine® (phenobarbital, passiflore: Procter & Gamble pharmaceuticals, Neuilly-sur-Seine, France), Pré-Par® (ritodrine: Solvay Pharma, Suresnes, France) and Salbumol® (salbutamol: Glaxo Wellcome, Paris, France) before delivery. She also took Maxilase-Bacitracine® tablets (alpha-amylase, bacitracin: Sanofi Winthrop, Gentilly, France) for a sore throat. 3 days later she presented with urticaria which was treated with Atarax® 25 mg/day and Polaramine® 2 mg/day (dexchlorpheniramine: Schering-Plough, Levallois-Perret, France). As soon as she started antihistamines, her urticaria worsened and became more pruriginous. 2 days later, she underwent a caesarian operation and other drugs were prescribed:

Syntocinon® (oxytocin: Sandoz, Rueil-Malmaison, France), Pro-Dafalgan® (propacetamol: UPSA, Rueil-Malmaison, France), Zinnat® (cefuroxime: Glaxo Wellcome, Paris, France), Profénid® (ketoprofen: Specia, Paris, France), Fragmine® (dalteparin sodium: Pharmacia, Saint-Quentin-Yvelines, France) and Parlodel® (bromocriptine: Sandoz, Rueil-Malmaison, France). After the delivery, a morbilliform eruption appeared. 7 days later, the patient presented with a fever of 40°C, adenopathy and erythroderma. Multiple microbiologic cultures and viral serologies eliminated infectious disease. 5 days after the discontinuance of all drugs except Parlodel®, the cutaneous lesions cleared.

Skin testing

Using Finn Chambers (Epitest, Tuusula, Finland), the 3 patients were tested with the European standard series, their topical medicaments and systemic drugs. All drugs, including Atarax®, were tested with a crushed tablet diluted in water. Prick tests were also performed with Atarax® tablets. A few months later, other patch tests were performed with different dilutions (2%, 5%, 10% aq.) of hydroxyzine hydrochloride and all the other components of Atarax® tablets: macrogol 6000 (5% aq.), colloidal silica (5% aq.), povidone K30 (5% aq.), microcrystalline cellulose (5% aq.), magnesium stearate (5% aq.), eudragit E (20% pet.), lactose (20% aq.), talc (as is) and titanium dioxide (5% aq.). They were also patch tested with piperazine (1% pet.), ethylenediamine (1% pet.), and triethanolamine (2.5% pet.) marketed by Isotec (Saint Quentin, France) and 6 other histamine H1-antagonists: dexchlorpheniramine (Polaramine®), loratadine (Clarityne®), chlorpromazine (Phénergan®), mequitazine (Primalan®), terfenadine (Teldane®) and cetirizine (Zyrtec®). Reading was performed 3 days later according to international convention. 190 control subjects were tested with Atarax® tablets.

Results

All 3 patients gave positive patch tests (+++) with Atarax® tablet and with the different dilutions of hydroxyzine (+++ or ++) (Fig. 1). All the other components of Atarax® tablet, and also the prick tests with Atarax®, were negative. Piperazine, ethylenediamine, triethanolamine and the 6 other antihistamines were negative. Patient no. 2 had a positive patch test (+) to tomato. Patient no. 3 had doubtful reactions to Natisédine® and Zinnat®. The 190 control subjects had negative patch tests with Atarax® tablet.

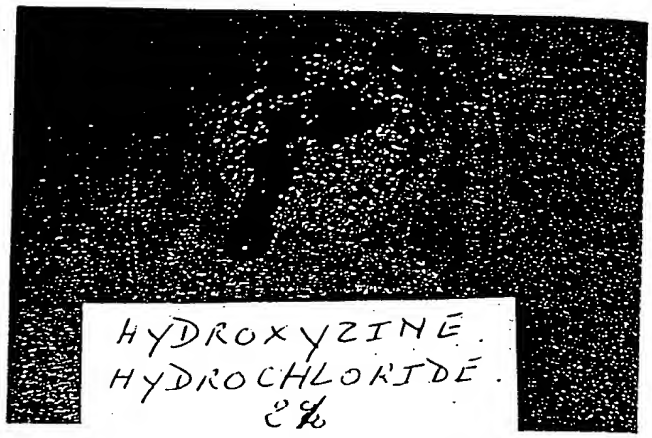

Fig. 1. Patient no. 3: positive patch test to hydroxyzine hydrochloride (2% aq.)

Discussion

Hydroxyzine is a 1st generation histamine H1–antagonist that is derived from piperazine. This drug also blocks muscarinic-cholinergic, α-adrenergic and 5-hydroxytryptaminergic receptors. It is an antiallergic drug but also a tranquillizer, a hypnotic and used as preoperative medication.

The 1st generation of histamine H1-antagonists is divided into 6 subgroups: alkylamine, ethanolamine, ethylenediamine, piperazine, piperadine and phenothiazine. They all have the basic structure of histamine modified by substitution on the imidazole ring. They have effects especially on H1-mediated reactions (3). Their side-effects are sedation, daytime drowsiness and neuroleptic effects. They also block other receptors : urinary retention, nasal stuffiness and blurring of vision are related to their anticholinergic properties (4). These adverse reactions have limited the use of the classical antihistamines. There are new 2nd generation H1-receptor antagonists that are more selective and less sedative. However, hydroxyzine is still widely used because of its availability in formulation for parenteral use, relatively high benefit-risk ratio and suitability for 1× daily administration.

Skin sensitization occurs with the use of ethylenediamine and phenothiazines (5–7), the latter also producing photosensitivity (8–10). Recently, skin reaction to terfenadine has been reported (11). Like all antihistamines, hydroxyzine can induce cutaneous sensitization, though very few cases have been reported (2, 4). The generalized polymorphous rash that our patients had after taking hydroxyzine was very difficult to differentiate from the initial one. All 3 patients initially presented with urticaria (nos. 1, 3) or eczema (no. 2), which necessitated the prescription of drugs including

Atarax®. Secondarily, another iatrogenic cutaneous eruption appeared; Atarax®, but also other drugs, could have been involved in the genesis of this 2nd eruption. Allergy to hydroxyzine was demonstrated by the positivity of patch tests (12). These tests seem reliable because there was no false positive reaction in 190 control subjects.

Topical and systemic use of antihistamines can both induce skin sensitization. In our patients it was probably systemic sensitization because topical hydroxyzine does not exist. Besides, 2 of them had taken Atarax® a few months before. Topical use of H1-antagonists often produces local sensitization. Cross-reactions between ethylenediamine, present in some creams, and the ethylenediamine H1-antagonists aminophylline and piperazine have been reported (13, 14). Fisher (1) has shown that there is cross-allergy between different groups of antihistamines because of their structural similarities. Therefore, patients sensitized to hydroxyzine, which is a piperazine antihistamine, are also sensitized to ethylenediamine. In contrast to other published cases, our patients had positive patch tests to hydroxyzine but negative tests with piperazine, ethanolamine and ethylenediamine. Many 1st and 2nd generation antihistamines' tests are negative, including cetirizine, which differs from hydroxyzine by an acid function. Allergy to antihistamines must be considered when cutaneous lesions worsen on antihistamine therapy.

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Address:

Dominique Leroy
Service de Dermatologie
Centre Hospitalier Universitaire
Avenue Georges Clemenceau
14033 Caen
France

Tel: 02 31 27 25 06
Fax: 02 31 27 25 11

EXHIBIT 3

Clinical and Experimental Allergy, 2000, Volume 30, pages 1161–1165

Warfarin treatment of chronic idiopathic urticaria and angio-oedema

R. PARSLEW, D. PRYCE*, J. ASHWORTH† and P. S. FRIEDMANN‡

*Royal Liverpool University Hospital, Department of Dermatology, Prescot Street, Liverpool, *Taunton and Somerset Hospital, Musgrove Park, Somerset, †Stepping Hill Hospital, Stockport, Manchester, and ‡Southampton General Hospital, Tremona Road, Southampton, UK.*

Summary

Background Chronic idiopathic urticaria is a disabling condition that does not always respond to antihistamine drugs and other agents are sometimes needed to control disease activity. Warfarin has demonstrated efficacy in single unblinded case studies [1] but has been dismissed by others [2].

Objective We investigated the effect of warfarin treatment in eight patients with chronic idiopathic urticaria unresponsive to antihistamines in an open study. Six of the eight patients responded to treatment and three had a dramatic response. These three were included in a double-blind placebo-controlled trial of warfarin therapy to confirm significant benefit from treatment.

Methods The three warfarin responders had their stable warfarin dose encapsulated and placebo capsules were provided. A double-blind placebo-controlled crossover trial was performed on each patient. Visual analogue scores recorded disease activity.

Results Comparison of visual analogue scores showed a significant benefit while on warfarin with a reduction in pruritus and angio-oedema.

Conclusion This is the first double-blind placebo-controlled study to show a response of chronic idiopathic urticaria to warfarin. The mechanisms of action are unclear and require further study.

Keywords: treatment, urticaria, warfarin

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Introduction

Chronic idiopathic urticaria is a common disorder characterized by recurrent urticarial weals of unknown origin for 3 or more month's duration. Typically there is a variable response to antihistamines and a tendency to spontaneous resolution; many patients are adequately treated by general practitioners. However there is a subgroup of patients in whom there is no tendency to improvement with time and who suffers severe urticaria often accompanied by angio-oedema, which is unresponsive to antihistamines. Some of these patients have an associated underlying disorder but most have no detectable abnormality. Severe urticaria is a debilitating condition and nonantihistamine treatments are limited by their lack of efficacy and/or risk of side effects. It has been suggested that some patients may respond to warfarin therapy [1] but this was questioned in a further study which showed no improvement [2]. The possibility that in some forms of urticaria proteases of the complement, kinin, and clotting or fibrinolytic systems are activated to generate vasoactive mediators encouraged us to examine the effects of warfarin in chronic idiopathic urticaria.

We first performed an open study of eight patients with treatment resistant urticaria who appeared to show significant clinical benefit. We then performed a double-blind placebo-controlled cross-over study on three of these patients and confirmed a major therapeutic response. To explore the underlying mechanism, patients were challenged with mast cell degranulating agents: compound 48/80 and histamine both on and off warfarin.

Correspondence: R. Parslew, Royal Liverpool University Hospital, Department of Dermatology, Prescot Street, Liverpool, L7 8XP, UK.

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Materials and methods

Open study

Initially eight patients with a clinical diagnosis of angioedema and chronic idiopathic urticaria without physical precipitating factors or systemic features were studied because their disease was resistant to full dosage of antihistamines. Urticarial vasculitis was not formally excluded by biopsy. All drugs including antihistamines were stopped 1 week prior to the trial. They were asked to assess their global symptoms on a daily basis using a 20-cm linear visual analogue scale where 0 = no symptoms and 20 = worst symptoms ever experienced. Global scores represented general disease activity and well-being. Mean scores were obtained by measuring the actual distance from the origin to the point marked on the scale by the patient. A new scale was used each day and the patients brought all the scales with them for weekly review. The pretreatment assessment period lasted for 3 months after which each patient was anticoagulated with warfarin (there were no clinical contraindications) to achieve an International normalized ratio (INR) between 2.0 and 2.5. Patients were assessed for a further 3 months on treatment and the relative visual analogue scores compared.

After a washout period where the INR returned to normal there was a further assessment of 2 months without treatment. Visual analogue scores were analysed with the Wilcoxon rank sum test as the data derived from the visual analogue scores was not an interval or ratio scale.

Effect of warfarin on response to histamine and compound 48/80

Histamine in doses of 15.6, 62.5, 250, 1000, 4000, and 16000 ng and saline control was injected intradermally into the volar forearm of patients. Weal diameter, skin fold thickness, determined by Harpenden callipers, and erythema, measured with a reflectance meter (Diastron) were compared whilst the patients were fully anticoagulated (INR 2.0–2.5) with warfarin and off warfarin with a normal INR. All patients were off antihistamine treatment for one week prior to challenge. Similarly the same subjects were challenged on and off warfarin with 5, 50, 500, 5000, and 50 000 ng of compound 48/80. Significance was determined with Students paired *t*-test.

Double-blind placebo-controlled study

Three patients from the open study showed dramatic clinical improvement in their symptoms. To confirm that this was a real effect due to therapy, a double-blind placebo-controlled trial was performed. The three patients described below had been shown to have a stable INR on their individual warfarin doses. In conjunction with the pharmacy department at the Royal Liverpool Hospital each patient had their daily individual warfarin dose put into one gelatine capsule. A placebo capsule, identical in appearance, was also provided and the patient took either according to a protocol held by the pharmacy. The trial was conducted in a double-blind placebo-controlled fashion with the pharmacy acting as the third party unblinded dispenser. Patients were randomly allocated to a series of four bottles of capsules – two active and two placebo which they could encounter in any order. There were enough capsules in each bottle for one month's supply taking one capsule a day.

Over the ensuing four months patients were asked to complete weekly 20 cm visual analogue scales to assess their angio-oedema and pruritus. Urticarial lesion number was not assessed. A weeks washout period was given after each change of treatment to allow for levels of warfarin to reach the therapeutic range or to allow levels to fall back to the normal range before scores were taken. Weekly blood for INR measurements were taken irrespective of treatment and were sent to an independent observer blinded to the protocol and treatment to ensure anticoagulation remained within safe limits. Patients were also examined weekly for clinical signs of disease activity and complications of warfarin treatment, but global scores by the examining physician were not made. At the end of the trial the code was broken and responses were compared with treatment groups. The data from the visual analogue scores were analysed statistically by use of the Wilcoxon rank sum test.

In an attempt to characterize this group of patients we performed additional tests. Whilst off all treatment for at least 1 week all patients were inoculated with autologous pretreatment serum as previously described to look for the presence of serum-derived mast cell degranulating factors [3].

Patients

Mr TW a previously fit 38-year-old man presented with a 3-year history of almost daily recurrent facial swelling especially around the eyes and frequent severe urticarial swelling on the body. Individual lesions would last for up to 24 h and fade without trace. There was no family history of urticaria or angio-oedema. He had tried many antihistamines unsuccessfully in standard and high dose and for the previous 2 months a combination of Cimetidine 400 mg b.d. and Loratidine 10 mg o.d. with no benefit. The urticaria was unrelated to any physical factors and all investigations including C1 esterase inhibitor levels and complement levels were normal. Initially he was admitted to hospital for an unsuccessful trial of a strict exclusion diet. Subsequently he was started on warfarin as described and he improved dramatically. Through trial and error it was found

that when his INR (normal = 1.0) fell below 2.0 his urticaria would flare but above this level he would remain virtually symptom free. He has now been controlled on 6 mg warfarin with an INR between 2 and 2.5 for the last 2 years with severe flares of his facial swelling/urticaria should his INR fall substantially. He has suffered no warfarin-related side effects. He agreed to take part in the double-blind placebo-controlled trial.

Mrs KD a 38-year-old lady had suffered from angio-oedema and urticaria for 5 years and during this time she was never completely free of lesions. Urticarial lesions occurred on any area of the body, unrelated to physical stimuli, would last for about 12 h and disappear. She was not helped at all by standard dose and even high dose (Loratidine 30 mg/day) antihistamines and she was otherwise well on no drugs. Routine blood tests, complement and C1 esterase inhibitor levels were normal. She was started on warfarin as a therapeutic challenge. Her symptoms quickly diminished so that by week 2 she was completely free of any lesions. She was stabilized on a steady warfarin dose and she agreed to take part in the double-blind placebo-controlled trial.

Mrs PQ a 54-year-old woman presented with a 3-year history of almost constant crops of urticarial weals on the body and recurrent pruritic facial swelling involving her eyes and mouth. Standard dose antihistamines coupled with cimetidine 800 mg per day limited the attacks to 3–4 per week but she still felt that this was intolerable. She was otherwise well, on no drugs and there was no obvious relationship with physical stimuli.

She was commenced on warfarin and her antihistamines were stopped. As her INR increased she slowly improved and she found that if her INR rose above 3.0 she was completely symptom free. However she developed a sub-conjunctival haemorrhage when her INR was 3.7 and whilst she subsequently had an INR between 2.0 and 2.5 her symptoms were reduced but tolerable. This necessitated warfarin 2 mg per day and at this point she agreed to enter the double-blind placebo-controlled trial.

Results

Open study

Six of the eight patients showed a good clinical response whilst on warfarin, two showed no clinical response. Overall using results from all eight patients in the open trial the benefit derived from warfarin was significant – mean visual analogue score of global symptoms before treatment 14.5 (SD 6.5); mean visual analogue score on treatment: 4.5 (SD 7.9). ($P = 0.017$ 96.1% CI −16 −3 Wilcoxon rank sum test).

There was no significant difference in cutaneous skin fold thickness, weal diameter or erythema measured by the reflectance meter to either histamine or compound 48/80 on or off warfarin. For example when comparing weal diameter 10 min after cutaneous challenge with histamine on and off warfarin results were not significantly different: $P = 0.06$ (Students paired t-test) see Fig. 1. After challenge with compound 48/80 there was no significant difference in weal diameter at 10 min: $P = 0.3$ (Students paired t-test) see Fig. 2.

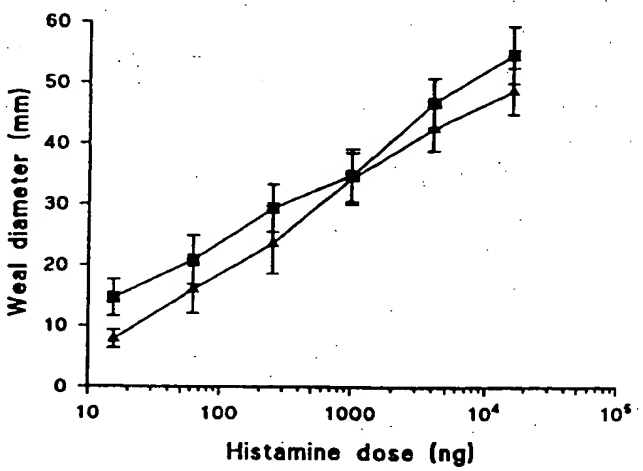

Fig. 1. Effect of warfarin on histamine weal diameter ($n = 8$). Off warfarin (■); on warfarin (▲).

Double-blind placebo-controlled study

Comparison of visual analogue results for angio-oedema on active and placebo treatment showed a significant benefit

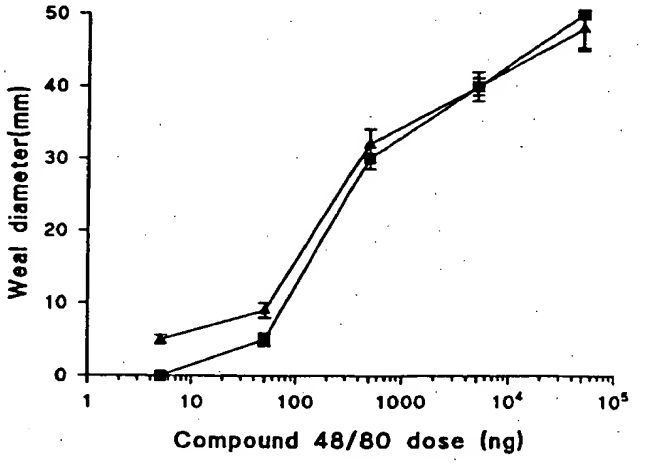

Fig. 2. Effect of warfarin on compound 48/80 weal diameter ($n = 8$). Off warfarin (■); on warfarin (▲).

while on warfarin: mean score on placebo, i.e. the two periods off active treatment was 17.67 whereas mean score on warfarin, i.e. the two periods on active treatment was 5.02 ($P = 0.031$ 96.9% CI−18–5.8 Wilcoxon rank sum test). Similarly, pruritus was greatly reduced: mean values of 16.97 for placebo and 5.05 for active treatment. ($P = 0.031$ 96.9% CI−21.6–6.7 Wilcoxon rank sum test). This confirmed a statistically significant benefit of warfarin treatment both for the angio-oedema and pruritus aspects of the condition.

In all three patients injection of autologous serum gave responses indistinguishable from saline control.

Discussion

The possibility that some patients with chronic idiopathic urticaria would derive clinical benefit from warfarin was originally suggested by Ryan [4] and supported clinically with anecdotal evidence [1,5]. Evidence supporting this was obtained in our open study in which six of eight patients with antihistamine resistant chronic idiopathic urticaria showed clinical benefit. However since chronic idiopathic urticaria is often a variable condition, showing periods of reduced activity or even spontaneous remission we felt it necessary to confirm this was a real therapeutic effect. Therefore a randomized placebo-controlled double-blind trial was performed on three of the patients who showed the most complete resolution of symptoms during the open study. This suggested that in these patients there was a significant beneficial effect of warfarin treatment. As shown with the formal challenge with histamine and compound 48/80, the effects of warfarin were not due to modification of responses to histamine and other mast cell mediators responsible for the acute weal and flare.

The known actions of warfarin are to reduce protein C concentrations and inhibit synthesis of vitamin K-dependent proteins in the clotting cascade (prothrombin and factors VII, IX and X). Warfarin acts as a competitive inhibitor of vitamin K and during the carboxylation of the precursors of these factors, vitamin K is converted to its inactive oxide and then metabolized back to its active form. Warfarin prevents this reconversion. The possibility that activation of clotting or fibrinolytic pathways as a mechanism in angioedema or urticaria was suggested by Ryan. He postulated that plasmin may contribute to the development of urticaria by removing the 'fibrin film wall', by activating complement and by increasing production of fibrin degradation products. However Smith *et al.* provided evidence against the involvement of plasmin [6].

The protein C/S anticoagulant pathway has been proposed to be a common link between coagulation and inflammation and an endothelial cell protein C receptor, modulated by inflammatory cytokines may play a part in this [7]. Activated protein C up-regulates interleukins 6 and 8 and may block neutrophil activation [8]. Warfarin inhibition of thrombin production also contributes to the anti-inflammatory action as in addition to short-term endothelial activation via P-selectin and platelet activating factor release stimulating early neutrophil adhesion and activation, thrombin induces E-selectin and interleukin 8 secretion in human vascular endothelium, facilitating a long acting pro-inflammatory response with neutrophil activation and extravasation [9]. There is convincing evidence that adhesion molecule expression is an important early event in chronic idiopathic urticaria and delayed pressure urticaria facilitating neutrophil infiltration of tissue [10]. Downregulation of these molecules by warfarin may impair vascular endothelial activation and lead to clinical improvement. It has been suggested that differential endothelial adhesion molecule expression may contribute to the pathogenesis of fleeting vs persistent weals [11] and it is of interest that in our patients the clinical impression was of a tendancy for benefit to be maximal against persistent angio-oedematous lesions rather than fleeting weals. This may indicate that warfarin preferentially downregulates certain adhesion molecules important in sustained urticarial/angio-oedema reactions.

Another possibility is that warfarin may modify effects of the proteases in the complement or kinin generating cascades. These processes are important in C1 esterase inhibitor deficiency when activation of C1 generates small vasoactive peptides resulting in vasodilatation and oedema. Also immune/allergic reactions can activate the kallikrein-mediated generation of kinins. One inhibitor of kinin production has been tried successfully in chronic urticaria (Trasylol) [10]. Trasylol inhibits certain proteolytic enzymes including kallikrein—an important kinin-derived from circulating prekallikrein. In high doses Trasylol suppresses C1 esterase and inactivates kallikrein precursors. This is helpful in hereditary C1 esterase inhibitor deficiency which gives rise to angioedema. Pre-kallikrein is activated by a variety of factors including factor XIIa and plasmin. One can easily hypothesize therefore that warfarin may inhibit plasmin activity thereby reducing activation of kallikrein and lowering the tendency to increased vessel permeability, tissue oedema and thus, urticaria. However, there is no evidence of raised kinin levels in urticaria or of low levels of endogenous inhibitors so the mechanism of action remains obscure. There is no doubt however, that our three patients derived and continue to have considerable benefit from the drug. They may represent a small subset of patients with chronic urticaria who respond favourably to this treatment though the mechanism is unknown. However we could not identify any features in these patients that would allow prediction of a good response to warfarin. In particular we could not detect the presence of mast cell degranulating factors in autologous serum in these patients, so this subset appears

not to have the anti-IgE receptor antibody. Further studies are required with larger numbers to determine the characteristics of those patients who do respond. Effects of warfarin on mast cell derived proteases, and the activation of platelets and leucocytes are potential targets. This may provide clues to the mechanism of the weal induction in these patients. If warfarin were to be used in the treatment of angio-oedema/urticaria, then its use should be limited to cases were conventional therapy has failed as the incidence of major haemorrhage is approximately 7% [12], although risk can obviously be minimized by avoiding anticoagulation in high risk cases such as alcohol abuse, chronic renal insufficiency and previous gastro-intestinal haemorrhage.

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EXHIBIT 4

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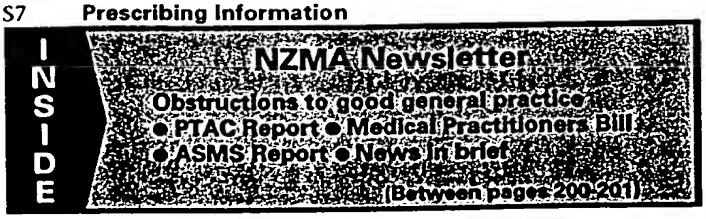

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to replace prophylactic immunisation. This shows ignorance of the principles of immunisation, one of the greatest success stories of medicine. Because we are host to a plethora of microbes which undergo constant mutation, frequently giving rise to pathogenic strains, we have immunity systems. These have evolved, by selection of reproductive advantage, to prevent the extinction of Homo sapiens by pestilence. The system makes us all different in immunological reactivity, exemplified by our rejection of allografts. When a new pathogen arises, its effects on us range from subclinical infection, through illness of varying severity, to death.

Both infection and immunisation lead to occasional autoimmune diseases, due to development of forbidden clones of lymphocytes which accidentally cross-react with a host antigen in mistake for a microbial one. The autoimmune diseases are potentially preventable by immunisations with vaccines which lack the host-cross-reactive antigens. This is being pioneered by Kehoe[1], who is developing a vaccine for rheumatic fever which lacks the host-cross-reactive antigens. Success in this research will save our vulnerable Maori children from rheumatic fever.

If measles immunisation is stopped, some children (particularly those with Maori type H genes)[2] will die of measles and some, like my sister-in-law, Romula Macfarlane, will die of autoimmune encephalomyelitis, which is 700 times more common after measles infection than after measles immunisation.[3,4] The argument applies to the other infectious diseases, including poliomyelitis where immunisation has abolished the previous tragic deaths and paralyses. Far from needing less immunisations, we need more, including new ones against AIDS, rheumatic fever, the other autoimmune diseases and the so-called "trivial" virus infections (Coxsackie, echo, adeno).

If measles immunisation is not lasting indefinitely, it simply needs to be repeated. Apart from immunisation's wonderful benefit in saving our loved ones from illness and death, it is the epitome of "cost effective" medicine.

Duncan Adams,
University of Otago Medical School, Dunedin.

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Skin reactions and terfenadine

Terfenadine is an H_1 receptor antagonist which is structurally dissimilar from other conventional antihistamines.[1] Along with other newer antihistamines (astemizole, loratadine and cetirizine), terfenadine has gained widespread popularity due to the lack of sedation as a side effect[2]. This group of antihistamines is nonsedating because they are lipophobic and hence do not readily cross the blood-brain barrier.[2] Serious cardiac arrhythmias have been associated with terfenadine and astemizole either in overdose or with concomitant administration of macrolide antibiotics or imidazole antibiotics.[3] Apart from this, the side effect profile of antihistamine medicines is generally of a minor nature.[3] Terfenadine has previously been associated with skin reactions, albeit rarely.[4,5] We present a case of terfenadine associated skin reaction.

A 53 year old woman was admitted with a 6 day history of generalised urticarial pruritic rash, especially the trunk and proximal parts of her limbs, itchy eyes and throat and some mild lip and periorbital swelling. She had a previous history of allergy to penicillins, erythromycin, some plant and grass species, and cats. This patient had suffered from a bee sting approximately 1 month previously and another bee sting 1 week prior to admission. Current medication history consisted of conjugated equine oestrogen tablets (Premarin) for 4–6 weeks, and terfenadine 60 mg twice daily commenced 4–7 days prior to the rash. These were hormone replacement therapy and selftreatment for rhinorrhoea respectively.

Treatment with intravenous hydrocortisone and oral promethazine brought little relief. After 2 days, treatment with terfenadine 60 mg twice daily was reintroduced, resulting in worsening of her rash and more swelling. Terfenadine was discontinued. The regimen was changed to loratadine, ranitidine and ketotifen with resolution of her symptoms over a 12 hour period.

Results of investigations showed raised acute phase protein (C-reactive protein = 66 mg/L), but were otherwise unremarkable including normal eosinophil count and C_4 level.

Whilst an anaphylactic reaction has been reported for intravenous administration of conjugated oestrogens,[6] we are unaware of reports of skin reactions to this medication.

Prior to discharge further inquiry revealed that she had had a previous hospital admission for an allergic reaction consisting of rash and painful joints. This had been attributed to Benadryl cough medicine, a proprietary preparation containing the antihistamine diphenhydramine and an expectorant, ammonium citrate.

The latent period between first intake of terfenadine and the onset of skin reactions is reported to be between three and seven days.[4] Based upon the temporal relationship between terfenadine administration and onset of rash, and the worsening of symptoms on rechallenge, we deduce that the most likely cause for this patient's hypersensitivity reaction was terfenadine.

AD McClintock
Pharmacy Department,
DWT Ching, C Hutchinson
Department of Medicine, Timaru Hospital, Timaru.

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The potential adverse effects of soybean phytoestrogens in infant feeding

It is well established that soybean products contain the phytoestrogens daidzein and genistein.[1-3] We have measured the levels of these compounds in several soy-based infant formulas available in New Zealand. The quantities recommended by manufacturers for infant feeding provide an intake (per kg body weight) of approximately three to five times as much daidzein and genistein than amounts which disrupt the menstrual cycle when fed to premenopausal women.[4] Exposure to phytoestrogens during soy-formula feeding is cause for considerable concern given the greater susceptibility of neonates to oestrogens and the likely duration of exposure through infancy.

The soy phytoestrogens act by (1) inhibiting the enzyme 17-ß-hyroxysteroid oxidoreductase, type 1, which converts the relatively impotent oestrone to the much more potent oestradiol; (2) occupying the oestrogen receptor, thus acting as antagonists to the naturally-produced oestradiol, inhibiting its effects (this behaviour is similar to that of another oestrogen agonist-antagonist, tamoxifen).[4] The consequent reduction in oestrogenic action appears to have a useful prophylactic effect against many oestrogen-dependent disorders in adults, including mammary and prostatic tumours.[5] However, the same effect is deleterious in infants. Considerable research has shown that adequate oestradiol is necessary for the imprinting and development of many physical, physiological and behavioural characteristics during the neonatal period and infancy.[6-7] Any decrease in the amount of oestradiol available is potentially harmful. Unfortunately, no specific research has investigated the effects of soy on these characteristics in the human infant, although it has been shown that phytoestrogens are absorbed similarly in infants and adults.[8]

It has been claimed that soy-formulas are unlikely to cause harm to infants because they have been used for years without adverse reports (O'Regan, personal communications, 1 February 1995). However, another oestrogen, diethylstilbestrol (DES), was administered extensively to women over three decades before the spectrum of harmful effects appeared, some manifesting themselves only when DES offspring reached adulthood.[9] Furthermore, although many women have consumed soy products without reports of problems, when a definitive experiment was conducted, consumption of 60 g of soy protein per day for 1 month disrupted the menstrual cycle during, and for up to 3 months after, administration.[4] Therefore the argument that no adverse effects were observed, therefore none occurred, is incogent. It is also plausible that harmful effects have occurred but have not been linked to soy consumption.

Other researchers have similar concerns about exposing young infants to phytoestrogens. The introductory paper presented by the USFDA Department of Health at a recent phytoestrogen conference notes 'phytoestrogens have some of the same capabilities to induce developmental toxicity as do other estrogens' and 'given the DES tragedy, it would be foolish to ignore the possibility that some phytoestrogens constitute a developmental hazard'.[10]

The New Zealand Ministry of Health has advised that parents 'continue to feed their infants soy-based milk formula if they have been advised to do so by their health specialists' (O'Regan, personal communications, 29 March 1995). However, soyformulas are available at supermarkets enabling parents to choose them without medical advice. It would be prudent for general sales of soy-formulas to be stopped. Failing this there is a need for information to be made available to both physicians and

EXHIBIT 5

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The current cardiac safety situation with antihistamines

Y. G. YAP and A. J. CAMM

Department of Cardiological Sciences, St George's Hospital Medical School, London, UK

Summary

Antihistamines (H_1-receptor antagonists) are amongst the most frequently prescribed drugs worldwide for the treatment of allergic conditions. The clinical interest of classical 'first generation' antihistamines is currently rather limited by their anticholinergic and sedative properties. The second generation of antihistamines, so-called non-sedating antihistamines, are free of these side-effects. However, since the 1990s, there have been reports that certain non-sedating antihistamines, mainly terfenadine and astemizole, might be associated with the risk of rare but severe dysrhythmias. These drugs prolong the monophasic action potential and surface electrocardiographic QT interval and may lead to the development of early after-depolarization and possibly torsades de pointes through an inhibition of potassium channel repolarization. Concomitant administration with drugs that inhibit the hepatic cytochrome P-450 (imidazole antifungals, macrolide antibiotics) or those that prolong the QT interval by the same or other mechanism (e.g. antiarrhythmics, antipsychotics, tricyclic antidepressants) increases their effect on the cardiac repolarization.

The cardiac safety profile of newer non-sedating antihistamines requires confirmation. Drugs with low or no potential to block the K+ rectification channel (e.g. IKr channels) are likely to possess cardiac safety advantages. Other drug-related factors such as the physico-chemical properties of the antihistamines and its metabolic profile may also contribute to the cardiac response.

Mizolastine is a new non-sedating antihistamine with antiallergic properties. It has a good bioavailability and a metabolism via the cytochrome P-450 oxidation accounting for only 35% of its hepatic clearance. In addition, mizolastine displays low lipophilicity and consequently low cardiac tissue fixation. In clinical studies, mizolastine has not shown any dose-related increase in QT intervals. Its clinical use has not been associated with ventricular dysrhythmias. Thus, although the post-marketing experience with mizolastine is still limited, mizolastine offers a safe alternative for the therapeutic management of allergic rhinitis and urticaria. However, more data are still needed on the cardiac safety of this and other non-sedating antihistamines.

Keywords: antihistamines, QT interval, torsades de pointes, ventricular repolarization

Introduction

Antihistamines (H_1-receptor antagonists) are one of the most frequently prescribed drugs worldwide for the treatment of allergic conditions such as seasonal allergic rhinitis, particularly in developed countries [1]. The use of first generation antihistamines, such as diphenhydramine, hydroxyzine, chlorpheniramine, brompheniramine and cyproheptadine, is limited by their anticholinergic and sedative properties. The second generation of antihistamines, so-called non-sedating antihistamines (e.g. terfenadine, astemizole, loratadine, cetirizine, acrivastine, mizolastine), are free of these side-effects. However, since the 1990s there have been some reports of syncope and torsades de pointes with certain non-sedating antihistamines, mainly terfenadine and astemizole [2–7]. As a result, terfenadine has recently been suspended in several European countries and the US Food and Drug Administration (FDA) is also considering possible suspension of terfenadine in the USA. The cardiac safety profile of the H_1 antihistamines

Correspondence: Dr Yee Guan Yap, British Heart Foundation Research Fellow in Cardiology, Department of Cardiological Sciences, St George's Hospital Medical School, Cranmer Terrace, London W4 3EL, UK.

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marketed in EEC countries is now being monitored by the European Health Authorities [8]. However, not all second generation H_1-receptor antihistamines seem to be associated with adverse cardiac toxicity. In this article, the cardiac effects of non-sedating antihistamines, including the novel non-sedating antihistamine, mizolastine, will be discussed.

The roles and mechanisms of ionic channels in arrhythmogenesis

The cardiac action potential is generated by the transmembrane movement of several ions currents, including Na+, Ca2+ and K+ in cardiac cells. Like all living cells, the inside of cardiac cells is negatively charged compared to the outside (resting transmembrane potential = –80 to –90 mV). However, cardiac cells are excitable and when appropriately stimulated, the ionic channels in the cell membrane open and close sequentially. This allows ions to travel back and forth leading to a change in the transmembrane potential, and hence the generation of an action potential (AP). The initial depolarization (phase 0) is triggered by a rapid influx of sodium ions (INa) which changes the cell potential from –90 to mV to + 30 mV [9]. At the following plateau phase (phase 2), the cell potential is maintained by the influx of calcium ions (ICa). The repolarization phase (phase 3) is driven predominantly by outward movement of potassium ions before the cellular potential returns to its resting state.

A variety of different K+ channel subtypes are present in the heart. The principal K+ currents participating in the repolarization of the AP in the heart under normal conditions are the delayed rectifier K+ current (IK) [10], the inward rectifier IK1 [11] and the transient outward K+ current (Ito) [12]. IK, the major time-dependent outward current, plays an important role in determining the duration of AP in many species. IK comprises two major separate current subtypes classified as IKr ('rapid') and IKs ('slow') [10]. Disturbances in any of these ionic movements may cause dysrhythmias. In this respect, IKr is most susceptible to pharmacological influence.

The initial cellular events that lead to dysrhythmias are due to the blockade of the IKr, which results in the prolongation of action potential duration and slowing of the repolarization. The prolongation of repolarization that precedes the subsequent activation of the inward depolarization current allows re-entry and induces an abnormality in the terminal repolarization, referred to as an early after-depolarization (EAD) [1,9], which is thought to be responsible for provoking a specific form of polymorphic ventricular tachydysrhythmia, i.e. torsade de pointes [1]. Such phenomena are more readily induced in the His-Purkinje network and also from a subset of myocardial cells from the midventricular myocardium, known as M cells [13].

Although it is not clear how the rhythmic activity arising from the early after-depolarization of the Purkinje fibre and M cells may lead to torsades de pointes, one theory is that the early after-depolarization may give rise to a premature action potential or a train of action potentials when the threshold for activation is reached. The resulting depolarizations, referred to as triggered activity may then induce an intramural re-entrant dysrhythmia, for example spiral reentry, with subsequently ever changing pathways of conduction (Fig. 1). Another theory is that the re-entrant dysrhythmia may be the result of an increase in spatial and temporal dispersion of repolarization and refraction within the ventricular wall (Fig. 1).

Since the late 1980s, there have been extensive investigations into the molecular structures of the various potassium channels subtypes. The elucidation of the molecular mechanisms underlying the different forms of congenital long QT syndrome has brought new insights into the mechanism of dysrhythmias associated with long QT. It has been recently shown that, there are at least six forms of congenital long QT syndrome, three fully characterized, two of which were directly linked to the mutation of the genes (HERG and KVLQT1/minK) encoding the two channels generating the rapid and the slow components of the delayed rectifier potassium

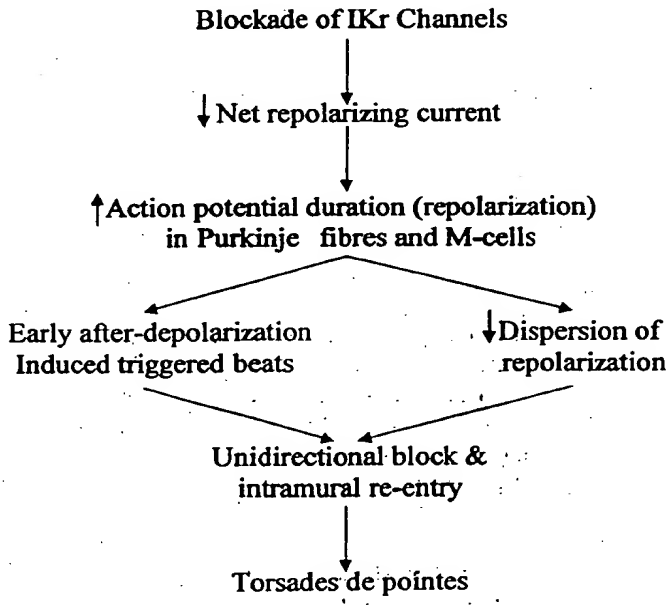

Fig. 1. Arrhythmogenesis of torsades de pointes.

currents, IKr and IKs, respectively [14,15]. The third form is linked to a mutation of the cardiac sodium channel, causing a delayed channel opening which leads to an excessive plateau-phase duration [16]. Therefore, sodium channel activation and potassium channel blockade represent different cellular mechanisms that may induce EAD and torsades de pointes. The IKr/HERG-delayed rectifier potassium currents are the primary target of class III antiarrhythmic drugs and of cardiotoxic antihistamines [17,18], However, as shown in patients with congenital long QT syndrome associated with the mutation of IKs/KvLQT1, blockade of other potassium channels, etc. may also be involved in the cellular events leading to QT prolongation and EADs.

Cloned human potassium channels subtypes proving extremely useful tools in the evaluation of potential cardiac effects of antihistamines. Among the antihistamines evaluated in IKr/HERG channels expressed in xenopus oocytes, astemizole, terfenadine and ebastine have shown blocking effects [19–21]. Mizolastine blocks IKr/HERG channels expressed in Chinese hamster ovarian cells, although in a reversible manner and at concentrations significantly higher than those corresponding to therapeutic free plasma levels (unpublished observations). Regarding the slow delayed rectifier channel (IKs), blocking effects have been reported in guinea-pig-dissociated ventricular myocytes with terfenadine and ebastine [19] but not mizolastine [22].

Thus, there are significant differences in the effectiveness of antihistamines in blocking the different members of the cardiac potassium channel family. It appears that those antihistamines such as terfenadine that suppresses simultaneously more than one channel involved in the lengthening of the action potential (i.e. IKr and IKs) and which blocks IKr at low concentration possesses higher propensity to induce dysrhythmias, whereas those that have minimal effects on a single channel are less likely to do so.

Prolongation of repolarization with antihistamines and torsades de pointes

The blockade of the potassium channels, tends to prolong ventricular repolarization, which manifests clinically as a prolonged QT interval and other T or U wave abnormalities on surface electrocardiogram. These abnormalities of repolarization predispose to the development of torsades de pointes. However, there is no linear relationship between the degree of QT interval prolongation and the likelihood of development of torsades de pointes. Furthermore, torsades de pointes can occur without a prolonged QT interval, and it does not develop in all patients with long QT intervals [23]. For instance, both quinidine and amiodarone are known to prolong the QT interval. While quinidine is a well recognized cause of torsades de pointes, amiodarone is rarely associated with torsades de pointes. Except in the case of congenital long QT syndrome, there have been very few data available to quantify the magnitude of arrhythmic risk assessment with particular values of QT prolongation, especially with drug-induced QT prolongation. In the case of long QT syndrome, data from the Long QT Syndrome Registry showed that the risk of malignant ventricular dysrhythmias is exponentially related to the length of QTc interval [24].

There is a characteristic initiating sequence prior to the onset of torsades de pointes, particularly in acquired torsades de pointes. The first ventricular complex of the sequence is usually of a ventricular ectopic beat or the last beat of a salvo of ventricular premature beats (Fig. 2). This is then followed by a pause terminated by a sinus beat. The sinus beat frequently has a very pro-longed QT interval and an exaggerated U wave. A premature ventricular beat then falls on the exaggerated U wave of the sinus beat and precipitates the onset of torsades de pointes. It has been suggested that in some patients, postpause accentuation of the U wave, if present, may be a better predictor of torsades de pointes than the duration of QTc interval [25], particularly with drug-associated torsades de pointes. When an ectopic beat or brief tachycardia is followed by a pause (Fig. 1), it is therefore important to examine the QT interval and T/U waves morphology in the postextrasystolic sinus beat [25].

Factors that may contribute to prolongation of ventricular repolarization

Causes of QT interval prolongation include the use of certain drugs, congenital long QT syndrome, ischaemic

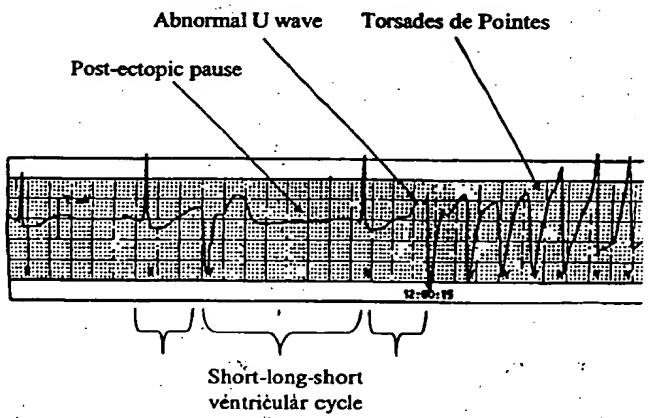

Fig. 2. Long-short ventricular cycle, pause-dependent QT prolongation and abnormal U wave leading to torsades de pointes.

heart disease, congestive heart failure, dilated cardiography, hypertrophic cardiomyopathy and myocarditis. Metabolic abnormalities such as hypokalaemia, hypocalcaemia and hypomagnesaemia can also cause QT interval prolongation. Thus, torsades de pointes is likely to occur in patients taking drugs known to prolong QT interval in the presence of these factors or bradycardia (which increase the amplitude of early after-depolarization). By far the most common cause of QT prolongation is a variety of drugs which are listed in Table 1.

The association of non-sedating antihistamines and torsades de pointes are reported mainly with terfenadine and astemizole. Some antihistamines exhibit their cardiac effects at therapeutic histamine-receptor blocking concentration, whereas others showed cardiac effects at supra-therapeutic concentration or have not shown

Table 1 Drugs that can prolong QT interval (this list is not comprehensive)

Antiarrhythmic drugs	Class 1a
	Quinidine
	Procainamide
	Disopyramide
	Ajmaline
	Class 1b
	Aprindine
	Mexilitine
	Class 1c
	Encainide
	Flecainide
	Class 3
	Amiodarone
	d, l-Sotalol, d-sotalol
	Bretylium
	Dofetilide
	Sematilide
Calcium channel blocker	Prenylamine (withdrawn)
	Terodiline (withdrawn)
Psychiatric drugs	Tricyclic and tricyclic antidepressant (amitriptyline, protriptyline, nortriptyline, imipramine, doxepin, maprotiline)
	Phenothiazines (thioridazine, chlorpromazine)
	Haloperidol
	Lithium
	Pimozide
	Chloral hydrate
	Sertindole
Antihistamines	Terfenadine (withdrawn in the USA)
	Astemizole
	Clarithromycin
	Ebastine
Antimicrobial and antimalarial drugs	Erythromycin
	Ketoconazole
	Pentamidine
	Quinine
	Chloroquine
	Halofantrine
	Amantidine
	Bactrim
	Spiramycin
	Sparfloxacin
Serotonin agonists/ antagonists	Ketanserin
	Cisapride
Other agents	Arsenic or organophosphates poisoning
	Probucol
	Tacrolimus

any significant cardiac effects. There are several structural factors that may be responsible for the varying cardiac action of antihistamines. Like Class III antiarrhythmic agents, certain antihistamines possess a diarylalkylamine moiety which is believed to inhibit the potassium channels [9]. Quaternization of diphenhydramine can result in a potent class I antiarrhythmic agent with long duration of action and notable tachycardia [9]. Lipophilicity of the side chain (nitrogen substitution) is also important in the potassium channel blocking activities of antihistamines [9]. In this aspect, mizolastine is less lipophilic compared with most of the antihistamines (loratadine, astemizole, ebastine, terfenadine) and does not contain either diarylakylamine nor diphenhydramine moieties. A low lipophilicity is reflected in a small volume of distribution [26–30 (Table 2), both characteristics being considered important for the cardiac safety profile of an antihistamine drug [31]. In addition, there are major differences in tissue distribution and myocardial fixation among H_1 antihistamines. A low apparent volume of distribution seems to be associated with low tissue fixation (i.e. tissue levels lower than blood levels). Heart/plasma ratios in animals are 4 in rats for terfenadine [32], 400 in dogs for astemizole [33], but only 0.5 for mizolastine in guinea-pigs (unpublished data). It is therefore important to note that the ability to cause QT prolongation and proclivity for producing torsades de pointes is seen only with some non-sedating antihistamines.

Terfenadine blocks the potasium channels; it is as potent as quinidine (which can also cause torsades de pointes) in inhibiting the delayed rectifier potassium channel [7,34]. Terfenadine undergoes rapid first-pass metabolism by cytochrome P-450 hepatic enzymes (CYP 3A4) and is transformed in its active metabolite terfenadine carboxylate. This metabolite terfenadine carboxylate had no effect on the potassium channel, even at high concentration [7]. Astemizole also blocks potassium channels and prolongs the QT interval [34], other antihistamines are less extensively studied [1].

Certain antimicrobial therapy including imidazole antifungals (ketoconazole, itraconazole) and macrolide antibiotics (erythromycin, clarithromycin) will inhibit the hepatic cytochrome P-450, which is responsible for the hepatic oxidative metabolism of terfenadine, resulting in an accumulation of the pro-drug [5,9]. In addition, drugs such as erythromycin and ketoconazole prolong the QT interval and erythromycin also inhibits the metabolic activity of hepatic cytochrome P-450. Concomitant administration of terfenadine and any of these antimicrobial therapies will produce marked QT prolongation that correlates with plasma concentration of unmetabolized terfenadine and increase the risk of dysrhythmia [1]. Concomitant administration of terfenadine with drugs that can inhibit metabolic activity of hepatic cytochrome P-450 or those that prolong QT interval must be avoided. Grapefruit juice contains a psoralen which also inhibits the metabolism of terfenadine by enzymes of the CYP3 A4 subfamily of cytochrome P450 and should also be avoided when taking terfenadine. In the case of astemizole, the P450 isoenzyme CYP3 A4 metabolizes the drug into two active metabolites, desmethylastemizole and norastemizole. The QT prolongation is mainly caused by astemizole and desmethylastemizole [9]. Ebastine, a highly lipophilic compound, is a pro-drug which is metabolized to a large extent through the cytochrome P-450. Mizolastine is less dependent on cytochrome P-450 hepatic metabolism than astemizole, terfenadine and ebastine [38–44] (Table 3). Thus, mizolastine has relatively little (1.5–50%) pharmacokinetic interactions with ketoconazole and erythromycin compared with the drugs mentioned above; the increase in mizolastine plasma concentrations, observed with systemic ketoconazole and erythromycin, led to plasma concentration equivalent to those obtained with a 15–20 mg dose of mizolastine alone.

Table 2 Physicochemical properties related to pharmocokinetic parameters

	Lipophilicity (Log P)†	Estimated volume of distribution (L/Kg) ††	References
Mizolastine	2.9*	1.4**	
Cetirizine	3.5	0.5	Spencer [26]
Loratadine	5.7	18	Haria [27]
Astemizole	5.8	45	Heykants [28]
Fexofenadine	5.3	9	Robbins [29]
Terfenadine	6.9	27	Lalonde [30]
Ebastine		7.2	N/A

† calculated values from compudrug, NA, Inc., Rochester NY 14682, USA;
†† calculated from references;
* measured = 3.3;
** measured volume of distribution after IV administration;
N/A not available.

Table 3 Metabolic characteristics of various antihistamines

	Bioavailability F (%)	Metabolic pathway		References
		Main (CYP)	Secondary (CYP)	
Mizolastine	65.5%	65% Glucuronidation	Hydroxylation (3A4, 2A6)	—
Cetirizine	97%			Wood (38)
Loratadine	14%	N-Dealkylation (34A,2D6)		Haria (27), Yumibe (39)
Astemizole	2%	O-Demethylation N-Dealkylation (3A4)	Hydroxylation (3A4)	Lavrijsen (40)
Terfenadine	1.6%	Oxidation, N-Dealkylation (3A4)	Oxidation to ketone (3A4)	— Lalonde (30), Ling (41), Yun (42)
Fexofenadine	≈ 70%			Robbins (29), Lippert (43)
Ebastine	Very low	Oxidation, N-Dealkylation	Further Oxidation	Stevens (44)

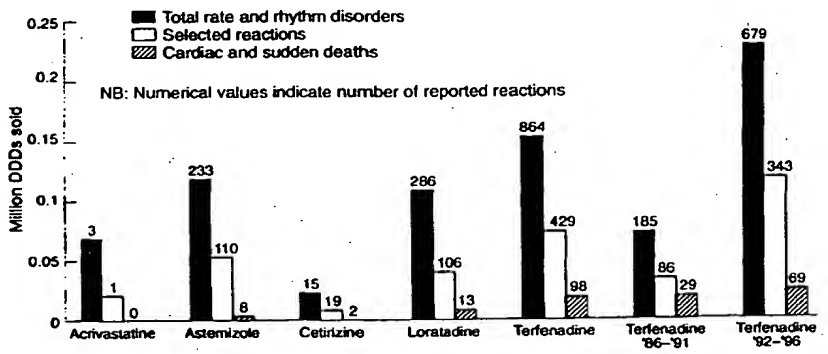

Fig. 3. Adverse reactions of non-sedating antihistamines (Adapted from Lindquist M, Edwards IR. Lancet 1997; 349: 1322.

Cetirizine has not been reported to cause any QT prolongation [1] but two cases of cardiac/sudden deaths have been reported from the WHO adverse drug reaction database (see below). Hydroxyzine does not seem to cause ventricular dysrhythmias although T-wave changes has been reported in patients treated with high doses (300 mg/day) [1]. There is no report of QT prolongation or ventricular dysrhythmias with ebastine or carebastine at therapeutic dosage [1]. Non-sedating antihistamines that do not block the IKr channels (e.g. fexofenadine) or block the channel with lower potency (e.g. cetirizine, loratadine) should be less cardiotoxic but this needs confirmation in further studies.

The WHO adverse drug reaction database provides a source of data on spontaneous adverse drug reactions from 17 countries where non-sedating antihistamines are available. Data reported includes total rate and rhythm disorders, selected reactions (QT prolongation, torsades de pointes, ventricular tachydysrhythmias, cardiac arrest and supraventricular tachycardia), cardiac and sudden deaths. Data from 1986 to 1996 reported 106 cases of selected reactions, 13 cardiac and sudden deaths for loratidine; 19 cases of selected reactions, two cardiac and sudden deaths for cetirizine; one case of selected reaction and no incidence of cardiac and sudden death for acrivastine [35]. When calculated as reports per million defined daily doses (DDD) sold, all three antihistamines have a very low reporting rate (Fig. 3). Specifically, the reporting rates for cardiac and sudden deaths were ≈ 0.005 for loratadine, 0.0008 for cetirizine and none for acrivastine compared with 0.038 for terfenadine. Although the reported incidences of deaths were themselves very low compared with terfenadine, the type of report and analysis has attracted some criticism for potential flaws and biases [36,37]. For instance, the report does not take into account the spontaneous rate of background cardiac events in the untreated population and the inclusion of a wide variety of cardiac events in a composite numerator, rather than specific ventricular events of relevance to non-sedating antihistamines. This makes the analysis questionable. The FDA, which monitors, analyses and reviews individual report and follow-up of cases of adverse drug reactions with antihistamines, did not find any

definitive causal association between loratadine, cetirizine or acrivastine and ventricular tachydysrhythmia up to 1997. Nevertheless, when antihistamines are widely prescribed for a self-limiting, non-fatal disease, the attributable risk must be assessed very carefully. It will also be very difficult to conduct a large controlled clinical study to examine the causal association between non-sedating antihistamines and ventricular dysrhythmias. Any crude adverse event report must be used in perspective and to detect trends and generate hypotheses that may guide surveillance and help plan future studies.

Effects of non-sedating antihistamines on QT intervals

The QT interval on the ECG is measured from the beginning of Q wave to the end of T wave. Conventionally, lead II has been used to measure the QT interval [45]. Several formulae may be used to correct the QT interval for the biophysical effect of heart rate (QTc). Of these, the most popular is that of Bazett's formula, but Fridericia's correction is preferred by some because it is more accurate at the extreme ranges of physiological heart rate [46]. There is otherwise little to choose between them. However, since the risk of torsade de pointes increases as heart rate slows, as does the uncorrected QT interval, but not the QTc, it is possible that the uncorrected QT interval may reflect the risk of dysrhythmia more closely than QTc, although this has not been formally tested [47]. QT prolongation is usually considered when the QTc interval is greater than 440 msec, although dysrhythmias are most often associated with values of 550 msec or more [48].

Currently the potential effects of any new H_1 antihistamines on human cardiac repolarization are carefully examined during its clinical development, mainly through the assessment of its potential to prolong the QT interval and the monitoring of potential cardiac events. An overview of the QT interval monitoring performed during the clinical development of mizolastine, showed that this new selective second generation H_1 antihistamine has no significant effect on cardiac repolarization in humans [49]. Mizolastine was administered orally up to 75 mg single dose and 40 mg repeated dose in healthy volunteers (i.e. 7.5 and 4 times the recommended daily dose, respectively) and at a dose of 10 or 15 mg in patients. In healthy volunteers, there was no increase incidence of QTc value > 440 ms or $\Delta QTc \geqslant 40$ ms compared with placebo. No dose-related increase in QTc interval was observed. The ECG parameters were not modified by the coadministration of mizolastine with digoxin, diltiazem and erythromycin, when compared to the effect of each coadministrated drug alone. The minor QT interval prolongation observed during the coadministration of ketoconazole with mizolastine ($\approx +7$ ms) might be attributable to the ketoconazole itself [50]. In patients, the mean QTc interval changes from baseline were not significantly different between mizolastine and placebo. In comparative studies vs. loratadine, a similar incidence of out-of-range values were observed with mizolastine and loratadine. There was little or no idiosyncratic QT interval prolongation in volunteers or patients receiving mizolastine. Mizolastine did not induce changes in T/U wave morphologies in humans. On the contrary, terfenadine was shown to prolong dose-dependently the ventricular repolarization [51]. In studies conducted in normal subjects, cetirizine [52] and loratadine [53] at supra-therapeutic doses were also devoid of an effect on cardiac repolarization. A mean 78 ms increase in QTc interval was reported when ketoconazole is coadministrated with terfenadine [5]; no other reports of QT monitoring of second generation antihistamines combined with ketoconazole have been published. Cetirizine, the metabolite of hydroxyzine, a first generation antihistamine which has been reported to be associated at high doses with T-wave changes, did not cause QT prolongation [1]. At therapeutic dosage, there has been no report of QT prolongation or ventricular dysrhythmia with ebastine [1].

The clinical experience with mizolastine, particularly in potentially high-risk patients, is still limited. However, no arrhythmic events have so far been documented in human subjects receiving mizolastine. Like other non-sedating antihistamines, extensive experience can only be gained by post-marketing surveillance. Nevertheless, mizolastine offers a safer alternative than terfenadine and astemizole.

Newer repolarization parameters such as QT dispersion (maximum–minimum QT intervals) on the 12-lead surface ECG which is an indirect measure of spatial heterogeneity of repolarization may be useful in assessing drug efficacy and safety. Patients receiving class 1a antiarrhythmic drugs who had torsades de pointes had significantly increased precordial QT interval dispersion [54]. In contrast, patients receiving amiodarone or class 1a antiarrhythmic without torsades de pointes, did not have increased QT dispersion. None of the patients with class 1a drug-induced torsades de pointes had recurrent torsades de pointes after being treated with amiodarone and showed no more increase in QT dispersion, although the QT interval prolongation remained [54]. QT prolongation, increased QT dispersion, marked morphological T-wave changes as well as female gender, ventricular ectopics, diuretics treatment, sequential bilateral bundle branch block and ventricular ectopics during treatment were recently reported to be predictors of torsades de pointes in patients with atrial fibrillation

or flutter exposed to the class III antiarrhythmic drug almokalant (an IKr blocker) [55]. Although amiodarone, quinidine and almokalant induce similar QT prolongation, amiodarone has less effect upon the dispersion of ventricular repolarization than the other two drugs and thus has less propensity to cause torsades de pointes. Thus, spatial heterogeneity/dispersion of the ventricular repolarization process may also be required together with QT prolongation for the genesis of torsades de pointes. Although the use of QT dispersion in the assessment of drug safety of non-sedating antihistamines has not been extensively evaluated, it should be noted that increase in QT dispersion has not been observed with mizolastine (unpublished observation).

Prevention of adverse cardiac effects of antihistamines

It is important to appreciate that drug-induced dysrhythmias are probably more likely in patients with a pre-existing prolonged QT interval, whether congenital or acquired (e.g. drug-induced, myocardial disease) [56]. Even in the absence of QT prolongation, there is probably a higher risk of dysrhythmias in patients with ischaemia or hypertrophy [56]. Electrolyte abnormality, including diuretic therapy may also increase the risk. In clinical practice, adverse effects of antihistamines can be prevented by not exceeding the recommended dose, avoiding their use in patients with a known or suspected heart disease (e.g. prolonged QT interval, A-V block, ischaemia, hypertrophy) and/or electrolyte imbalance such as hypokalaemia. Antihistamines with hepatic metabolism are to be avoided in patients with significant hepatic improvement, while those with a renal elimination should be avoided in case of renal insufficiency. Concomitant administration with drugs that inhibit the cytochrome P-450 (e.g. imidazole antifungals, macrolide antibiotics) or those that prolong the QT interval (e.g. antiarrhythmic, antipsychotics, tricyclic antidepressants) should also be avoided. It is advisable that high-risk patients (known heart disease, known long QT syndrome, etc.) prior to commencing any non-sedating antihistamines, particularly those that have been known to cause torsades de pointes, should have a baseline ECG to detect any pre-existing QT prolongation, myocardial ischaemia or hypertrophy. Non-sedating antihistamines that can cause QT prolongation and/or torsades de pointes should be avoided in such patients.

Conclusions

Non-sedating antihistamines are widely prescribed for the treatment of allergic conditions for their lack of anticholinergic and sedative effects. However, certain non-sedating antihistamines such as terfenadine and astemizole are now known to cause QT prolongation and torsades de pointes, particularly in overdosage or when imidazole antifungal agents or macrolide antibiotics are concomitantly ingested. Mechanistic studies have shown that the cardiac toxic effects of terfenadine and astemizole are due to the inhibition of repolarizing potassium channels, particularly IKr which leads to prolongation of the action potential and the QT interval, and to the development of early after-depolarizations, which trigger torsades de pointes. A novel non-sedating antihistamine with antiallergic properties, mizolastine has not shown any dose-related increase in the QT interval, idiosyncratic QT prolongation or ventricular dysrhythmia in phase II–III studies and may offer a safer alternative. More data are still needed on the cardiac safety of many non-sedating antihistamines which should be obtained by post-marketing surveillance and careful reviews of all individual reports of cardiotoxic effects.

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EXHIBIT 6

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GOODMAN & GILMAN'S The PHARMACOLOGICAL BASIS OF THERAPEUTICS

Ninth Edition

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Systemic therapy with *griseofulvin* is more effective for moccasin and vesicular bullous disease, and is followed by long-term topical therapy with the azoles and allylamines. Itraconazole, fluconazole, and oral terbinafine combined with a topical azole or terbinafine may replace griseofulvin therapy in the future.

Onychomycosis. Fungal infection of the nails is most frequently caused by dermatophytes but also can be caused by molds and *Candida*. Mixed infections are common. The nail must be cultured prior to therapy, since 30% of nail problems that appear clinically to be onychomycosis are actually due to psoriasis or another dystrophic nail condition (Achten and Wanet-Rouard, 1978). Onychomycosis serves as a reservoir for dermatophytes and contributes to treatment failure and recurrence of tinea pedis.

Oral therapy is necessary for onychomycosis, although the agents currently available, griseofulvin and ketaconazole, have limited efficacy. Treatment of onychomycosis of toenails with griseofulvin for 12 to 18 months produces a cure rate of 50% and a relapse rate of 50% after 1 year (Davies *et al.*, 1967). Results with ketaconazole are equally disappointing, and there is the additional worry of hepatotoxicity. Terbinafine, itraconazole, and fluconazole offer significant potential advantages. They quickly produce high drug levels in the nail, which persist after therapy is discontinued. Additional advantages include a broader spectrum of coverage with itraconazole and fluconazole and few drug interactions with terbinafine. Cure rates of 75% and greater have been achieved with all three drugs, with a shorter duration of treatment than for standard therapy (Gupta *et al.*, 1994a, 1994b). Intermittent regimens with itraconazole (1 week per month) and fluconazole (1 day per week) are undergoing evaluation.

Antiviral Agents

The armamentarium against viral infections unfortunately remains small. The major antiviral drug, *acyclovir*, frequently is used to treat cutaneous herpes simplex, herpes zoster, and chickenpox. The approval of *famciclovir*, a prodrug of penciclovir, and the potential approval of *valacyclovir*, a prodrug of acyclovir, may decrease the length of postherpetic neuralgia in patients. Intralesional injection of interferon alfa-2b is administered for condylomata acuminata. Improvement of psoriasis in AIDS patients with oral zidovudine has been reported. These drug are discussed in Chapter 50.

ANTIHISTAMINES

Histamine is present in mast cells, basophils, and platelets. After release, histamine binds to both H_1 and H_2 receptors in cutaneous vessels, although cutaneous injection of H_1 receptor agonists causes itching, whereas injection of H_2 agonists does not. Complete blockade of H_1 receptors does not totally relieve itching, and some studies suggest that combinations of H_1 and H_2 receptor blockers may be superior to H_1 blockers alone (Bleehen *et al.*, 1987). Older H_1 receptor antagonists have some anticholinergic activity and are sedating. Newer H_1-type antihistamines (*terfenadine, astemizole,* and *loratadine*) lack anticholinergic side effects and are nonsedating, largely because they do not cross the blood-brain barrier. *Cetirizine, acrivastine,* and *temelastine* currently are undergoing review by the FDA or are in clinical trials. H_2 receptor blockers include cimetidine, ranitidine, famotidine, and nizatidine. Besides their use in combination with H_1 receptor blockers for pruritus, the H_2 receptor blockers have immunomodulating effects and have been used in children to treat warts (Orlow and Paller, 1993). Tricyclic antidepressants act on both H_1 and H_2 receptors and have been used to treat pruritus and urticaria.

Antihistamines are frequently used in dermatology to treat pruritus due to urticaria, atopic dermatitis, contact dermatitis, psoriasis, and many other conditions. The newer, nonsedating H_1 receptor blockers are as effective as older H_1 blockers such as hydroxyzine and do not cause tachyphylaxis (Monroe, 1993). Nonsedating antihistamines should not be coadministered with medications that inhibit cytochrome P450 activity, such as ketoconazole or erythromycin, because drug interactions have occasionally been associated with cardiac arrhythmias.

The pharmacology of histamine antagonists is covered in detail in Chapter 25.

TOPICAL ANTIPSORIASIS DRUGS

Psoriasis is a chronic scaling skin eruption characterized by keratinocyte hyperproliferation. It affects 1% of the population of the United States and has a genetic basis. While there is no cure, multiple therapies exist with various modes of delivery (*see* Figure 64–1). Corticosteroids (discussed previously), calcipotriene, and anthralin are topical therapies reserved for localized disease.

Calcipotriene

Calcipotriene (DOVONEX), a vitamin D analog, was approved for the topical treatment of psoriasis in 1994. Chance observation of improvement of psoriasis in an osteoporotic patient receiving an oral derivative of 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D$], the hormonally active

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United States Court of Customs and Patent Appeals.
Application of Bernard L. ZENITZ.
Patent Appeal No. 7142.

July 9, 1964.

Proceeding on application for patents relating to chemical compounds said to be useful as hypotensive agents, antinauseants, antipyretics and sedatives. The Board of Patent Appeals, Serial No. 746,615, rejected claims 3, 5, 9 through 12 and 21 and appeal was taken. The Court of Customs and Patent Appeals, Worley Chief Judge, held that claims 3, 9, 10 and 11 were not obvious but that claims 5, 12 and 21 were properly rejected.

Modified.

West Headnotes

[1] Patents 51(1)
291k51(1) Most Cited Cases

[1] Patents 66(3)
291k66(3) Most Cited Cases
United States patent speaks for all it discloses as of its filing date, even when used in combination with other references. 35 U.S.C.A. § 103.

[2] Patents 51(1)
291k51(1) Most Cited Cases
Knowledge inconsistent with allowance of claim of patent application need not be limited to disclosure of identical invention. 35 U.S.C.A. § 103.

[3] Patents 16(3)
291k16(3) Most Cited Cases
(Formerly 291k18)
Question of patentability was not what prior art inventor was aware of at time he made his invention, but whether his invention would be obvious in view of state of art at time it was made. 35 U.S.C.A. § 103.

[4] Patents 113(6)
291k113(6) Most Cited Cases
That tranquilizer was a better one than that previously disclosed in that it minimized side effects of hypotensive activity must be considered in determining patentability of claimed compound. 35 U.S.C.A. § 103.

[5] Patents 16.25
291k16.25 Most Cited Cases
(Formerly 291k18)
Claims 3, 9, 10 and 11 of patent application dealing with chemical compounds said to be useful as hypotensive agents, antinauseants, antipyretics and sedatives were unobvious as to hydroxypropyl derivatives and corresponding hydroxy-ethyl and hydroxy-lower-alkyl derivatives and were patentable. 35 U.S.C.A. § 103.

[6] Patents 16.25
291k16.25 Most Cited Cases
(Formerly 291k18)
Claims 5, 12 and 21 of compounds said to be useful as hypotensive agents, antinauseants, antipyretics and sedatives were unpatentable as obvious. 35 U.S.C.A. § 103.

Patents 328(2)
291k328(2) Most Cited Cases
2,921,069, 2,928,767, 2,926,164. Cited.
****925 *746** Laurence & Laurence, Washington, D.C. (Dean Laurence, Herbert I. Sherman, Washington, D.C., of counsel), for appellant.

Clarence W. Moore, Washington, D.C. (George C. Roeming, Washington, D.C., of counsel), for the Commissioner of Patents.

Before WORLEY, Chief Judge, and RICH, MARTIN, SMITH, and ALMOND, judges.

WORLEY, Chief Judge.

Zenitz appeals from the affirmance by the Board of Appeals of the rejection of claims 3, 5, 9 through 12 and 21 of his patent application. [FN1]

The appellant deals with chemical compounds described as 10-piperidinoalkylene derivatives of trifluoromethyl phenothiazines which are said to be useful as 'hypotensive agents, antinauseants, antipyretics and sedatives.' Claim 3 reads:

'3. A pharmacologically acceptable acid-addition salt of a compound having the formula

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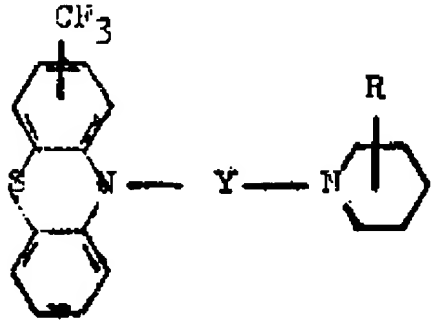

wherein Y represents lower-alkylene containing at least two carbon atoms separating the nitrogen atoms and R represents hydroxy-lower-alkyl.'

The references are:

*747

Ullyot	2,921,069	January 12, 1960	(filed April 9, 1956)
Cusic et al.	2,926,164	February 23, 1960	(filed August 1, 1956)
Gulesich et al.	2,928,767	March 15, 1960	(filed July 17, 1957)
Belgian Patent	551,400	March 29, 1957	
Craig et al.	J.Org.Chem., Vol. 22, pages 709-11 (June 1957)		

Cusic, the primary reference, discloses compounds identical to those claimed except for a chloro (Cl) substituent in place of the trifluoromethyl (CF(3)) substituent in the claimed compounds. The secondary references establish that prior to the filing date of Zenitz's application the art was fully aware of the substitution of Cl and CF(3) potentiating groups in phenothiazines analogous to those now claimed by Zenitz.

The examiner held, and the board agreed, that the substitution of CF(3) for Cl in the phenothiazines disclosed by Cusic, would be obvious to one of ordinary skill in the art.

Zenitz contends that the Cusic, Gulesich and Ullyot patents are not available as **926 references for an obviousness rejection under Section 103 because they issued on applications which, although filed earlier than his, were copending therewith. Zenitz maintains that he could not have been aware of the Cusic or Gulesich disclosures at the time he filed his application.

[1] This court has held in a number of decisions that a United States patent speaks for all it discloses as of its filing date, even when used in combination with other references. In re Kander, 312 F.2d 834, 50 CCPA 928; In re Gregg, 244 F.2d 316, 44 CCPA 904; In re Seid, 161 F.2d 229, 34 CCPA 1039.

[2][3] In re Harry, 333 F.2d 920, 51 CCPA, , decided concurrently herewith, holds that 35 U.S.C. § 103 is in parimateria materia with 35 U.S.C. § 102(e) and points out that the latter section was intended to enact the rule of Alexander Milburn Co. v. Davis-Bournonville Co., 270 U.S. 390, 46 S.Ct. 324, 70 L.Ed. 651, wherein the court said:

'* * * The delays of the patent office ought not to cut down the effect of what has been done. The description shows that Whitford was not the first inventor. Clifford had done all that he could do to make his description public. He had *748 taken steps that would make it public as soon as the Patent Office did its work, although, of course, amendments might be required of him before the end could be reached. We see no reason in the words or policy of the law for allowing Whitford to profit by the delay and make himself out to be the first inventor when he was not so in fact, when Clifford had shown knowledge inconsistent with the allowance of Whitford's claim. * * *'

Although in Milburn, Clifford disclosed the same invention claimed by Whitford, the criterion was that Clifford had shown knowledge inconsistent with the allowance of Whitford's claim. That such knowledge need not be limited to a disclosure of the identical invention is shown by a later decision of the Supreme Court, Detrola Radio & Television Corp. v. Hazeltine Corp., 313 U.S. 259, 269, 61 S.Ct. 948, 952, 85 L.Ed. 1319 (1941) wherein the Court states:

'We conclude that Wheeler accomplished an old result by a combination of means which, singly or in similar combination, were disclosed by the prior art and that, notwithstanding the fact he was ignorant of the pending applications which antedated his claimed date of invention and eventuated into patents, he was not in fact the first inventor, since his advance over the prior art, if any, required only the exercise of the skill of the art.'

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The question is not what prior art Zenitz was aware of at the time he made his invention, but whether his invention would be obvious in view of the state of the art at the time it was made.

We therefore proceed to the question whether the differences between Zenitz's invention and the state of the art at the time the invention was made, here assumed to be Zenitz's filing date, are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art to which said subject matter pertains.

Zenitz submitted affidavits by Wylie and by Luduena to show that his compounds have unexpected properties. The affidavits compare the tranquilizing activity and hypotensive effect of hydroxy and hydroxypropyl piperidyl propyl trifluoromethyl phenothiazine derivatives of Zenitz with the corresponding chloro compounds of Cusic. The examiner allowed Zenitz's claims to the hydroxy but not to the hydroxy propyl derivatives. Claims 3, 9, 10 and 11 on appeal are drawn to those hydroxy propyl derivatives. Claims 5, 12 and 21, however, are drawn to compounds having an acyloxy-lower-alkyl substituent, e.g. an acetate. As to the latter compounds the examiner said:

'* * * Note also that appellant has not compared the instant compounds**927 against those of Cusic et al. shown to have particularly good tranquilizing activity, viz. the acetates * * *.'

As to those compounds which have been compared, the Luduena affidavit confirms the following conclusion of Wylie:

'Moreover, I have noted that not only are the trifluoromethyl compounds considerably more active as tranquilizers and sedatives than the corresponding *749 chloro and unsubstituted compounds as shown above but also show considerably less undesirable side effects, such as a hypotensive effect, making them superior with respect to decreased side effects than either the corresponding chloro compounds or the unsubstituted compounds. a hypotensive effect alone is useful in compounds that are to be used specifically to lower the blood pressure, but when this property is also possessed by compounds used as tranquilizers or sedatives, it is regarded as a serious side-effect which can cause other side-effects such as dizziness or blurring of vision. Its minimization or complete elimination in compounds to be used as sedatives and tranquilizers is, therefore, to be desired.'

The examiner considered the affidavits and said:

'* * * Patentability has been consistently urged during prosecution upon this newly introduced 'surprising separation of hypotensive and tranquilizing properties' which was not disclosed in the specification as filed. The specification at page 21 merely indicates that results indicate their use as hypotensive agents, antinauseants, antipyretics and sedatives. * * *'

Since the separation of hypotensive from tranquilizing effect was not originally disclosed, the examiner, citing In re Stewart, 222 F.2d 747, 42 CCPA 937, held that Zenitz could not now rely on that effect as a ground for establishing unobviousness. The board agreed.

A case much in point is Westmoreland Specialty Co. v. Hogan, 167 F. 327, CCA 3 (1909). The patent there involved a celluloid top for a dredge for holding salt. The patentee discovered subsequent to the issuance of his patent that the celluloid top had the advantage that it did not conduct moisture from the atmosphere to the salt in the cellar. The court said:

'* * * It is true that at the time this patent was applied for the particular process of moisture supply from a metal cap and the insulating capacity of celluloid to stop it were not stated, or, indeed, known to the patentee. He knew metal caps would oxidize, and substituted celluloid to stop oxidation, and such use has shown that the stoppage of oxidation resulted in keeping the salt dry. But the mere failure of a patentee to realize all the benefits and possibilities of his invention is not fatal. The after-discovery of unsuspected usefulness in a disclosed apparatus, far from detracting from its value, may serve to enhance it. It is the benefits which test, use, and time unfold that really determine merit. * * *'

In the case before us Zenitz disclosed his compounds to be useful as tranquilizers as well as hypotensives, sedatives, etc. It is true he made no mention of the separation of hypotensive and tranquilizing activity, but as with the celluloid top in Westmoreland, the advantage of minimized hypotensive activity would inherently flow from the indicated use of the compounds as tranquilizers.

The present facts are to be distinguished from those in the *750 several cases cited by the solicitor [FN2] to support the contention that appellant is not in a favorable position to urge undisclosed **928 properties as a ground for establishing unobviousness. One of those cases, In re Herr, 304 F.2d 906, 907, 50 CCPA 705, involved certain testosterone derivatives. The affidavit presented evidence of oral anabolic and androgenic activity. The specification was devoid, however, of any mention of such activity for the compounds and the sole utility disclosed in Herr's

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specification was that the compounds were useful intermediates in the making of other compounds which had anabolic and androgenic activity. It is readily seen that if the disclosure of Herr was followed the compounds would be used as intermediates and no benefit from their anabolic and androgenic activity would flow from such use. Here, Zenitz disclosed a tranquilizer and subsequently established that if it is used as a tranquilizer it is a better one for it minimizes the side effects of hypotensive activity. Therefore we think the latter property must be considered in determining the patentability of the claimed compound.

[5] We find the affidavits establish unobviousness as to the hydroxypropyl derivatives and the corresponding hydroxy-ethyl and hydroxy-lower-alkyl derivatives. Therefore, we are obliged to reverse as to claims 3, 9, 10 and 11.

[6] As to compounds having acyloxy-lower-alkyl, none of which have been compared, we are unable to find support in the record for concluding that proof of unobviousness of the compounds having hydroxy alkyl substituents establishes that the corresponding compounds wherein the hydroxy alkyl substituents are esterified, are also unobvious. [FN3] We therefore affirm the rejection of claims 5, 12 and 21 as being obvious from the corresponding compounds of Cusic in view of the secondary references showing that Cl and CF(3) are commonly employed potentiating groups on compounds of the type here claimed.

The rejection of claims 3, 9, 10 and 11 is reversed.

The rejection of claims 5, 12 and 21 is affirmed.

***746** Modified.

FN1. Serial No. 746,615, filed July 7, 1958.

FN2. In re Milton E. Herr, 304 F.2d 906, 907, 50 CCPA 705; In re Lundberg, 253 F.2d 244, 45 CCPA 838; In re Crawford, 250 F.2d 370, 45 CCPA 750; In re Rossi, 241 F.2d 726, 44 CCPA 750; In re Stewart, 222 F.2d 747, 42 CCPA 937; In re Dalzell et al., 166 F.2d 834, 35 CCPA 1024; Abbott et al. v. Coe, 71 App.D.C. 195, 109 F.2d 449.

FN3. Unfortunately Zenitz's brief does not help any. The entire discussion of the actual facts before us is relegated to the following paragraph:
'THE SUBJECT MATTER INVOLVED
'The structure of the compounds on appeal can be seen from the claims on appeal * * *. Their relationship to the references is described in the Examiner's Answer * * *. No further chemical details are here offered because they are unnecessary to decide any issue in this case.'

52 C.C.P.A. 746, 333 F.2d 924, 142 U.S.P.Q. 158

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EXHIBIT 8

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C

Ex parte Sasajima, Ono, Nakao, and Yamamoto

Patent and Trademark Office Board of Appeals

Opinion dated Nov. 20, 1980

Patent No. 4,303,663 issued Dec. 1, 1981

United States Patents Quarterly Headnotes

PATENTS
[1] Patentability -- Composition of matter (§ 51.30)
Initially undisclosed relative toxicity of compound that is not viewed as property that is ordinarily separable from its disclosed use as pharmaceutical must be considered in determining claims' patentability; prima facie obviousness is rebutted and rejection reversed where that property of claimed compounds is totally unexpected from record.

PATENTS
Particular patents -- Butyrophenone Compounds
Sasajima, Ono, Nakao, and Yamamoto, Novel Butyrophenone Compounds, rejection of claims 6, 7, 25, and 26 reversed.

***103** Appeal from Art Unit 121.

Application for patent of Kikuo Sasajima, Keiichi Ono, Masaru Nakao, and Hisao Yamamoto, Serial No. 795,145, filed May 9, 1977, division of application, Serial No. 568,819, filed Apr. 17, 1975. From decision rejecting all claims, applicants appeal (Appeal No. 420-36).

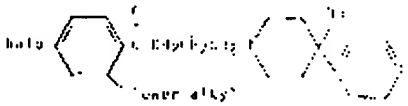
Raymond C. Stewart, Falls Church, Va., for appellants.

Before Serota and Blech, Examiners-in-Chief, and Pellman, Acting Examiner-in-Chief.

Pellman, Acting Examiner-in-Chief.

This is an appeal from the examiner's decision finally rejecting claims 2, 3, 4, 6, 7 and 21 through 26, all of the claims in the application. However, since by amendment, claims 2, 3, 4 and 21 through 24 have been cancelled, only claims 6, 7, 25 and 26 are before us for consideration.

The subject matter on appeal involves certain butyrophenone derivatives (claims 6 and 7) and neuroleptic or analgesic compositions containing the ketone compounds (claims 25 and 26). These compounds have the structure:



To illustrate the claims on appeal, claim 6 is reproduced as follows:

> 6. 1-[y-(2-Lower alkyl-4-halobenzoyl)propyl]-4-(3-trifluoromethyl phenyl)-4- hydroxypiperi dine, or a pharmaceutically acceptable acid addition salt thereof.

In her answer, the examiner cites the references listed below:

Janssen	3,518,276	June 30, 1970
Katsube et al.	3,922,266	Nov.25, 1975
(Katsube)		(filed Dec. 18, 1972)
Yamamoto et al.	3,936,468	Feb. 3, 1976
(Yamamoto)		(filed Feb. 15, 1973)
Sasajima et al.	3,979,390	Sep. 7, 1976

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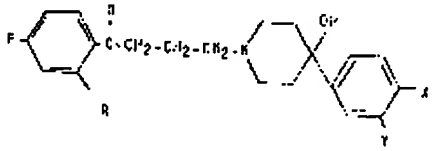
(Sasajima) (filed Mar. 16, 1973)

***104** All of the claims stand rejected for being unpatentable (35 U.S.C. 103) over the obvious structural variants shown in the references, i.e., Katsube, column 8, lines 62-63 (Haloperidol) and 64-65 (Triperidol); Yamamoto, column 4, lines 36-37 (Haloperidol) and 38-39 (Triperidol); and Janssen, column 1, lines 50-53 (Haloperidol) and Example XV (Haloperidol with a 2-methyl group on the 4-fluorobenzoyl moiety). The Sasajima reference (column 7, lines 19-22) has also been mentioned as showing related butyrophenone compounds. Appellants do not appear to deny that the claimed compounds and compositions would have been prima facie obvious. Rather, they rely upon the declaration of Dr. Hideaki Fukushima, comparing the relative effectiveness of the claimed compound with those of the prior art, and the declaration of Dr. Toshiya Inukai, supplying data as to the comparative toxicity and therapeutic index for the tested compounds.

We have considered all of the evidence presented, as well as the arguments of appellants and the examiner. Although we have no doubt that the examiner has established a strong inference of obviousness, the declaration showings are believed adequate to rebut said inference. Consequently, the rejection will not be sustained.

For ease of discussion, the data in the declarations, which have been tabulated by appellants, is shown below with reference to the generic formula:



Compound	R	X	Y	EDsub50	LDsub50	LDsub50 / EDsub50
Appellants	CHsub3	H	CFsub3	0.20	450	2250
Janssen	CHsub3	Cl	H	> 10		
Haloperidol	H	Cl	H	0.55	260	473
Triperidol	H	H	CFsub3	0.25	50	200

In concluding that the demonstrated difference in activity was not unexpected, the examiner, at page 3 of the answer, notes that Triperidol is shown to be over twice as effective as Haloperidol. Since the only difference between these two compounds is a 3-CF3 group (Triperidol) instead of a 4-Cl substituent (Haloperidol) on the phenyl ring, the examiner reasons that the corresponding change on the Janssen compound would reasonably be expected to produce a similar increase in effectiveness. It is then pointed out that the EDsub50 for the instant compound is, in fact, substantially the same as that for Triperidol.

Although the examiner acknowledges that the toxicity of the claimed compound is significantly less than that of the prior art homologs and analogs, she apparently gives this property no weight because it has not been disclosed in the specification. To support her position, the examiner cites the decision in In re Davies et al., 475 F.2d 667, 177 USPQ 381 (CCPA 1973).

Superficially, the rationale in the Davies et al. case, supra, would seem to be applicable herein. That is, the public would derive the most benefit from those patents which clearly disclose the advantages that are ultimately persuasive of unobviousness. Nevertheless, the court's preliminary remarks are particularly relevant to its holding. Thus, at 177 USPQ 385, Judge Almond, speaking for the court, observes:

> "It is difficult to see how one skilled in the art could conclude that the unexpected properties of improved gloss, transparency and processability find a basis in or inherently flow from the disclosure in the application that the toughened polystyrene has improved mechanical properties such as impact strength and the like."

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In the present case, we do not view the relative toxicity of a compound as a property that is ordinarily separable from its disclosed use as a pharmaceutical. More analogous to the situation herein is the holding in In re Zenitz, 52 CCPA 746, 333 F.2d 924, 142 USPQ 159 (1964). In this decision, the court, after stating that originally undisclosed minimized hypotensive activity would inherently flow from the indicated use of the compounds as tranquilizers, at 52 CCPA 750, explains that:

> "Here, Zenitz disclosed a tranquilizer and subsequently established that if it is used as a tranquilizer it is a better one for it minimizes the side effects of hypotensive activity. Therefore we think the latter property must be considered in determining the patentability of the claimed compound."

[1] Accordingly, like the court, we also think that the initially undisclosed property ***105** at issue, i.e., low toxicity, must be considered in determining the patentability of the appealed claims. Since we find said property of the claimed compounds totally unexpected from this record, the prima facie obviousness is rebutted and the rejection cannot stand.

The examiner's decision rejecting claims 6, 7, 25 and 26 is reversed.

Reversed.

P.T.O. Bd.App.

212 U.S.P.Q. 103

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EXHIBIT 9

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C

United States Court of Customs and Patent Appeals.
In the Matter of the Application of Gerald E. KOLLMAN and Elwood N. Irwin.
Appeal No. 78-624.

March 15, 1979.

A decision of the Patent and Trademark Office Board of Appeals affirmed rejection of claims in application serial number 547,292 for "Synergistic Herbicidal Composition." On appeal by the applicant, the Court of Customs and Patent Appeals, Baldwin, J., held that: (1) in view of fact that patent cited as prior art not only failed to highlight claimed composition of herbicide compound among many disclosed but made no suggestion of required FENAC/diphenyl ether ratio which was found by appellant to possess unexpected activity or synergism, there was improper rejection of certain claims on ground of anticipation; (2) where, even if each of applicant's examples showed presence of unexpected result, examples would not provide adequate basis for conclusion that great numbers of compositions recited in particular claims would behave in the same way, such claims were properly rejected for obviousness, and (3) claims 7 and 8 for combinations of FENAC and diphenyl ether for use as a herbicide showed, through process of extension of trend which could be ascertained by one having ordinary skill in the art, unexpected effectiveness, and were improperly rejected for obviousness.

Affirmed as to some claims and reversed as to others.

West Headnotes

[1] **Patents** 66(1.12)
291k66(1.12) Most Cited Cases
In view of fact that cited patent not only failed to highlight claimed composition of herbicide compound among many disclosed but made no suggestion of required FENAC/diphenyl ether ratio which was found by appellant to possess unexpected activity or synergism, there was improper rejection of claims on ground of anticipation. 35 U.S.C.A. § 102.

[2] **Patents** 16.25
291k16.25 Most Cited Cases
(Formerly 291k18)
Where individual herbicides embraced by patent applicant's combination had been known, and prior art disclosed that original species could be combined with many known herbicides including compound "FENAC," it was necessary, in determining obviousness issue, only to determine whether examples were of sufficient weight to overcome teachings of such prior art, and where, even if each example showed presence of unexpected result, examples would not provide adequate basis for conclusion that great numbers of compositions recited in particular claims would behave in same way, such claims were properly rejected for obviousness. 35 U.S.C.A. § 103.

[3] **Patents** 17(2)
291k17(2) Most Cited Cases
(Formerly 291k18)
Synergism, in and of itself, is not conclusive of unobviousness, in that synergism might be expected. 35 U.S.C.A. § 103.

[4] **Patents** 16(3)
291k16(3) Most Cited Cases
(Formerly 291k18)
Unobviousness of broader claimed range can in certain instances be proven by narrower range of data, and if one having ordinary skill in art is able to ascertain trend in exemplified data which would allow him to reasonably extend probative value thereof, proof thus considered might then be sufficient to rebut Patent and Trademark Office Board of Appeals holding of prima facie obviousness. 35 U.S.C.A. § 103.

[5] **Patents** 16.25
291k16.25 Most Cited Cases
(Formerly 291k18)
Patent application claims 7 and 8 for combinations of FENAC and diphenyl ether for use as herbicide showed, through process of extension of trend in exemplified data, which could be ascertained by one having ordinary skill in art, unexpected effectiveness, and were not unpatentable for obviousness. 35 U.S.C.A. § 103.

Patents 328(2)
291k328(2) Most Cited Cases
2,977,212, 3,401,031, 3,484,230, 3,798,276. Cited.
***49** Terence P. Strobaugh, Philadelphia, Pa., for appellants.

Joseph F. Nakamura, Washington, D. C., for the

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Commissioner of Patents; Gerald H. Bjorge, Washington, D. C., of counsel.

Before MARKEY, Chief Judge, and RICH, BALDWIN, LANE and MILLER, Judges.

BALDWIN, Judge.

This appeal is from the decision of the Patent and Trademark Office (PTO) Board of Appeals (board) affirming the rejection of claims 1 and 3-15 [FN1] in appellants' application serial No. 547,292, filed February 5, 1975, for "Synergistic Herbicidal Composition."

> FN1. We note that claims 3-9 are dependent upon claim 2, a claim cancelled during the prosecution of this application. For the purposes of this appeal, we treat claims 3-9 as containing the limitations of claims 1 and 2.

The board affirmed the examiner's rejection of all claims under 35 U.S.C. s 103 as unpatentable "over the teachings of Bayer et al., Poignant et al., Inoue et al., and Tischler." The board also entered new rejections, pursuant to its authority under 37 C.F.R. 1.196(b),[FN2] of the claims under 35 U.S.C. ss 103 or 102 over Bayer et al. We reverse the decisions of the board concerning the s 102 rejection of all claims and the s 103 rejection of claims 7 and 8, and affirm its decision regarding the s 103 rejection of the remaining claims.

> FN2. 37 C.F.R. 1.196(b) provides, in pertinent part, that:
> (b) Should the Board of Appeals have knowledge of any grounds not involved in the appeal for rejecting any appealed claim, it may include in its decision a statement to that effect with its reasons for so holding, which statement shall constitute a rejection of the claims.

The Invention

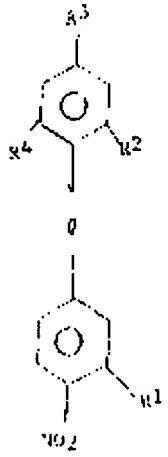
Appellants have found that certain herbicidal compositions containing 2,3,6- trichlorophenylacetic acid (hereinafter FENAC) and certain diphenyl ethers exhibit desirable activity when used against nutsedge (or Cyperus) weeds.

The following claims are illustrative of the invention:

1. A synergistic herbicidal composition comprising (A) 2,3,6- trichlorophenylacetic acid, or an agronomically acceptable salt, ester, or amide thereof, and (B) a diphenyl ether herbicide, wherein the weight ratio of (A) to (B) is about 1:10 to about 20:1.

3. The composition of claim 2 (sic) wherein the weight ratio of (A) to (B) is about 1:1 to about 4:1.

5. The composition of claim 4 wherein the diphenyl ether has the formula



***50** wherein R 1 is a hydrogen atom, a (C 1-C 4) alkoxy group, a carboxy group, a carb (C 1-C 4) alkoxy group, or a carb (C 1- C 4) alkoxy (C 1-C 4) alkoxy group,
R 2 is a chlorine atom or a nitro group,
R 3 is a chlorine atom or a trifluoromethyl group, and
R 4 is a hydrogen atom, a chlorine atom, or a fluorine atom.

6. The composition of claim 3 wherein the diphenyl ether is 2,4- dichlorophenyl 4-nitrophenyl ether.

7. The composition of claim 3 wherein the diphenyl ether is 2-chloro-4- trifluoromethylphenyl 3-ethoxy-4-nitrophenyl ether.

8. The composition of claim 3 wherein the diphenyl ether is 2-chloro-4- trifluoromethylphenyl 3-carbomethoxy-4-nitrophenyl ether.

10. A method of controlling weeds which comprises applying to the weeds a composition according to claim 1 in a herbicidally effective amount.

Issue

The dispositive issues in this case pertain to whether the examples in the specification are demonstrative of unobvious results and, further, whether those unobvious results are sufficient to overcome the s 103 rejections.

The Prior Art

The following references were applied against the claims:

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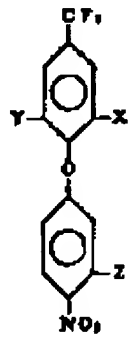
Bayer et al.	Patent No.	3,798,276 issued on March 19, 1974.
Poignant et al.	Patent No.	3,484,230 issued on December 16, 1969.
Inoue et al.	Patent No.	3,401,031 issued on September 10, 1968.
Tischler	Patent No.	2,977,212 issued on March 28, 1961.

Bayer et al. (hereinafter Bayer) discloses diphenyl ethers having the general formula:



wherein

X is a hydrogen atom, a halogen atom, a trihalomethyl group, an alkyl group, or a cyano group,

Y is a hydrogen atom, a halogen atom or a trihalomethyl group, and

Z is an alkoxy group, an alkoxyalkoxy group, a hydroxyalkoxy group, an alkyl group, a halogen atom, an alkylamino group, a dialkylamino group, an alkylthio group, a carboxy group, a carbalkoxy group, a carboxyalkyl group, a carbalkoxyalkoxy group, a carboxyalkyl group (sic), a carbalkoxyalkyl group, a dialkylureido group, an alkylamino group, or a carbalkoxyamino group,

as a herbicide effective against a number of weeds including the monocot nutsedge (Cyperus). Bayer also suggests that these diphenyl ethers be mixed with other herbicides including, Inter alia, FENAC.

The other references are cumulative in technical content to Bayer and need not be discussed in detail.

It is noted, however, that Poignant et al. (hereinafter Poignant) mentions a test which is said to show up the presence of "synergism" in combination herbicides:

> This test (was) * * * disclosed by Colby in the magazine "Weeds," January 1967, pp. 20-22.
>
> Let us resume the principle of said method:
>
> Assuming X 1 is the percentage of plants not killed by herbicide A at the dose p, and Y 1 is the percentage of plants ***51** not killed by herbicide B at the dose q, the "expected" percentage, E 1, of plants not killed by the mixture (A 🔑 B) at the dose (p 🔑 q) is:

$$E_1 = \frac{X_1 \cdot Y_1}{100}$$

Then, it is only necessary to compare E 1 with the actual percentage, E, of plants not killed by (A 🔑 B) at the dose (p 🔑 q) to know the character of the combined action of the two herbicides.

If E 1 is higher that E, there is synergy. In the opposite case, there is antagonism.

Background

Appellants' brief before the board presented the following argument:

Initially, applicants concede that each of the components

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of the claimed compositions is a known herbicide. Thus, in order to establish the patentability of their compositions, applicants must show that the combination of those known herbicides produces a composition having unexpected properties.

In the specification of the present application, applicants have presented three tables of data * * * showing the effectiveness of compositions of the invention against yellow and purple nutsedge at various rates and ratios, together with comparative data showing the activity of each of the individual components of the composition used alone at the same rate as each is present in the compositions. This data demonstrates that the herbicidal activity of the claimed compositions against nutsedge is greater than the expected additive activity of each of the components used alone. For example, in Table I, [FN3] diphenyl ether I used alone at 4 lb/A controlled 50% Of yellow nutsedge, while fenac used alone at 2 lb/A controlled 0% Of yellow nutsedge. Unexpectedly, a Combination of 4 lb/A of diphenyl ether I with 2 lb/A of fenac controlled 99% Of yellow nutsedge, rather than 50% Control which would be expected from merely additive activity. Similarly, *52 in a typical example of Table II [FN4] diphenyl ether III used alone at 1/2 lb/A controlled 60% Of yellow nutsedge, while fenac used alone at 1 lb/A controlled 10% Of yellow nutsedge. However, the Combination of 1/2 lb/A of diphenyl ether III and 1 lb/A of fenac controlled 85% Of yellow nutsedge, rather than the 70% Control which would be expected if the activity of the individual components was just additive. Numerous additional specific examples are set forth in the table which also show this unexpectedly good activity for compositions in which the ratio of diphenyl ether to fenac varies from 1:16 to 16:1. Thus, while one skilled in the art would expect that the two individual components of the claimed compositions would act upon the plants independently and give at best an additive herbicidal effect, the data presented in the tables reflects a coaction between the two components when used together to produce significantly greater than additive herbicidal activity.

FN3

TABLE I

ACTIVITY AGAINST YELLOW NUTSEDGE (Cyperus esculentus)

(% Control - two weeks after treatment)

		Fenac (lb./A)					
Ether	(lb./A)	0	1/4	1/2	1	2	4
I	0	0	0	0	10	0	20
I	1	40	70	70	70	90	--
I	2	50	60	70	70	99	--
I	4	50	60	90	95	99	--
I	8	60	--	--	--	--	--
II	0	0	--	--	0	10	40
II	1/8	15	--	--	78	93	--
II	1/4	45	--	--	88	97	--
II	1/2	50	--	--	93	99	--
II	1	75	--	--	--	--	--
III	0	0	--	--	0	10	40
III	1/8	20	--	--	80	95	--
III	1/4	45	--	--	99	95	--
III	1/2	50	--	--	90	100	--
III	1	78	--	--	--	--	--

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FN4

TABLE II

ACTIVITY AGAINST YELLOW NUTSEDGE (Cyperus esculentus)

(% Control - four weeks after treatment)

Ether	Fenac (lb./A) (lb./A)	0	1	2	4
II	0	0	10	15	25
II	1/8	10	80	100	--
II	1/4	30	99	100	--
II	1/2	40	100	100	--
II	1	65	--	--	--
III	0	0	10	15	25
III	1/8	30	95	95	--
III	1/4	25	99	99	--
III	1/2	60	85	100	--
III	1	85	--	--	--

The examiner responded to these arguments in the Answer:

> Appellants point to various examples of data presented in the specification as establishing synergism at other than the 1:1 ratio. This position is not well taken. This data satisfies but part of the criteria set to determine if synergism exists. For instance appellants point to the test in table I employing 4 lbs. of the ether in combination with 2 lbs. of fenac. However there is no testing of the ether at 6 lbs. nor the fenac at 6 lbs., i. e. no testing of the individual components at the total amount of the combination employed.
>
> The legally accepted definition of synergism as meaning "the combined action of two or more agents . . . that is greater than the sum of the action of one of the agents used alone" is cited in In re Luvisi et al., (342 F.2d 102, 109), 144 U.S.P.Q. 646. In re Lemin et al. (408 F.2d 1045), 161 U.S.P.Q. 288 points out the necessity of presenting data for each component singly at the total rate applied *53 in combination in addition to the fact that each component must be tested individually at the rate at which it appears in combination.
>
> Thus, other than in the case of the active ingredients employed in a 1 to 1 ratio the data is not seen to satisfy the requirements necessary to establish synergism.

The board agreed with the examiner that the exemplified data were insufficient to overcome the s 103 rejection, but did so for substantially different reasons:

> As we have indicated hereinbefore, we have found the comparative data in Appellants' specification insufficient to negate the prima facie case of obviousness presented by the Examiner's application of the prior art. We do not agree with the Examiner's statement that the only data supporting synergism occurs at a 1:1 ratio of the active ingredients. Nor do we agree that it is always necessary to show testing of individual components at a Total amount corresponding to the total of combination employed. We find the data nonpersuasive for a variety of reasons. First, there is no indication that a statistically significant number of test plants or replicates was employed. The test procedure described in the specification at pages 9-10 does not even provide any actual number of plants per flat or any number of flats. Nor do we find data, in a statistically significant number or otherwise, supporting the allegations of synergism over the entire range claimed by Appellants of 1:10 to 20:1 of Fenac: diphenyl ether. In Table I an unexpected result is indicated at ratios of 1 Fenac to 2, 4 and 8 of either I. Synergism may also be indicated at proportions 1:1 using ether VI and ether VII. Similarly, there is a showing at 1:2 and 1:4 in Table III,[FN5] again using ether I.

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FN5

TABLE III

ACTIVITY AGAINST PURPLE NUTSEDGE (Cyperus rotundus)

(% Control - two weeks after treatment)

Ether	(lb./A)	Fenac (lb./A) 0	1/4	1/2	1	2	4
I	0	0	0	0	0	10	20
I	1	0	20	20	30	30	--
I	2	30	40	50	90	80	--
I	4	40	50	60	70	80	--
I	8	50	--	--	--	--	--

The board entered a new rejection of the claims under s 102 or s 103 as unpatentable over Bayer and added:

> Turning to our new rejection under 35 U.S.C. 102/103 in view of Bayer et al., even were all the data in the specification statistically significant, persuasive of synergism, and free of all the criticisms we have made, still the showing would not be relevant to refute the strong prima facie case of obviousness presented by this patent of Appellants' assignee. None of the showings of record compares for herbicidal effectiveness the Bayer et al. diphenyl ethers in combination with Fenac * * * its adjacent homolog (the corresponding benzoic acid compound * * *) or any other of the listed carboxylic acids and derivatives, to demonstrate that Appellants' specific combinations as claimed, within the specific but very broad weight ratios claimed, have such synergistic effects as to provide more than the "additional advantages and effectiveness" expected by the patentees.

Appellants argued in a request for reconsideration that the s 102 rejection was improper since:

> ***54** (T)he Bayer et al reference fails to provide any suggestion that such (disclosed) "additional advantages and effectiveness" would be other than the expected additive effect against individual weeds of combining two known herbicides or the expected complementary activity of two known herbicides which have different spectra of activity. The Bayer et al patent further fails to give any suggestion that combinations of diphenyl ethers and 2, 3, 6- trichlorobenzoic acid would be Expected to be synergistic. To infer such suggestions from the Bayer et al disclosure would turn the world upside down by assuming that synergistic or greater than additive activity would Normally be expected from a combination of conventional herbicides by those skilled in the art. Since applicants (sic) compositions represent a selection of a specific known herbicide from among many known herbicides, and a selection of specific ratios for this known herbicide and the diphenyl ether, and in claims 4 to 8 even the selection of specific subgenera and species of diphenyl ether herbicides. (sic) (,?) They define a class of herbicidal compositions which is not taught by the Bayer et al patent, and are thus not anticipated under 35 U.S.C. 102.

With regard to the s 103 rejection, appellants argued that the board recognized that the data demonstrated "that certain compositions of diphenyl ethers and FENAC do possess unexpected activity or synergism." Appellants then argued that the showing of "unexpected results"

> for proportions of ether I at 1:2 and 1:4 with fenac * * * * fully supports the patentability of claim 6, which is directed solely to combinations of ether I in proportions of fenac of 1:1 to 1:4. Thus, it is believed that the decision of the Board supports the Reversal of the first rejection of claim 6.
>
> The data presented in Tables I and II is at least as conclusive a showing of unexpected results or synergism for ether II as for ether I. For example, in Table I, the data shows fenac to be essentially inactive against yellow nutsedge at one pound/acre, and ether II to provide 50% Or less control of this weed at rates of 1/8, 1/4, and 1/2 pound/acre. However, combinations of fenac, at one pound/acre with ether II at 1/8, 1/4, and 1/2

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pound/acre all provide control of yellow nutsedge significantly in excess of 70%. The data in Table II involving ether II provides even more compelling evidence of unexpected activity. Moreover, although no specific data is provided for 1:1 ratio of ether II and fenac in Tables I or II, one skilled in the art would certainly extrapolate the data presented in these tables and conclude that similar unexpected control of nutsedge would be obtained, for example, with a composition of one pound/acre of ether II and one pound/acre of fenac. Thus, it is believed that the data when read in the light of the Board's decision supports the Reversal of the final rejection of claim 7.

The Board has also questioned whether the data is "statistically significant." However, no guidance has been provided by the Board to allow applicants to determine whether the herbicidal data set forth in the application would meet any standards of significance which the Board might apply. The Board nevertheless has apparently been provided with sufficient data to allow them to state unequivocally that certain of the test results are unexpected. * * * Regardless of the question of statistical significance, it would seem that art-recognized tests carried out by trained scientists and incorporated into a patent application should be believed by the Patent and Trademark Office in the absence, as in the present case, of any evidence to Doubt the correctness of the test results or their statistical significance. (Emphasis in original.)

OPINION

Section 102 Issue

[1] The board indicates that it considers our decision in In re Schaumann, 572 F.2d 312, 197 U.S.P.Q. 5 (Cust. & Pat.App.1978) as mandating a finding that the claims are anticipated by Bayer. We do not agree.

***55** In Schaumann, appellants claimed a specific compound within a prior art (Hildebrandt's) genus. There it was observed:

> In response to appellants' primary argument that the general formula of Hildebrandt's specification cannot constitute an anticipation of every one of the one hundred and five or more compounds encompassed thereby, the examiner noted that the method disclosed by Hildebrandt for producing -(meta-hydroxyphenyl)-isopropylamines would result only in the production of secondary amines, thus limiting to fourteen the number of possible compounds taught by the reference. That number is further reduced to seven, said the examiner, if one considers the preference for lower alkyl secondary amines expressed in claim 1 of the reference.

Id. at 314, 197 U.S.P.Q. at 7.

We agreed, noting:

> When we consider also that claim 1 of the Hildebrandt patent, read in conjunction with the signification given the expression "alkyl radical" in the specification, embraces a very limited number of compounds closely related to one another in structure, we are led inevitably to the conclusion that the reference provides a description of those compounds just as surely as if they were identified in the reference by name. Since one of the compounds thus described is HEP (the claimed species), we agree with the examiner and the majority of the board that appellants' right to a patent thereon is barred under 35 U.S.C. 102(b).

Id. at 316, 197 U.S.P.Q. at 9.

In the case at hand, even disregarding the fact that Bayer fails to highlight the claimed composition among the many dozens disclosed, it is apparent there is no suggestion of the required FENAC/diphenyl ether ratio. Accordingly, we reverse the s 102 rejection.

Section 103 Issue

[2] Appellants note in their brief that they

> had conceded that the individual herbicides embraced by appellants' combination were known * * *. Bayer et al discloses that its original species (the diphenyl ethers) could be combined with many known herbicides including the compound 2,3,6-trichlorophenylacetic acid which is the compound "Fenac."

Thus, we need only determine whether the examples are of sufficient weight to overcome the teachings of Bayer. Appellants' assertion that those examples overcome the PTO's holding of obviousness has at least some merit.

As a starting point, we recognize that even if each of the examples showed the presence of an unexpected result, those examples would not provide an adequate basis for concluding that the great numbers of compositions recited in generic claims 1, 3-5 and 9-15 would behave in the same way. See In re Greenfield, 571 F.2d 1185, 197 U.S.P.Q. 227 (Cust. & Pat.App.1978), and cases cited therein. Hence, we affirm the holding of the board with regard to these claims.

However, the data said to support the patentability of species claims 6-8 require further analysis.

[3] One issue that need be considered is the very presence of unobvious results in the data.[FN6]

> FN6. Often during the prosecution of this application in the PTO and, indeed, in the

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> arguments presented to this court, the term "synergism" is applied without qualification. Synergism, in and of itself, is not conclusive of unobviousness in that synergism might be expected. In re Huellmantel, 324 F.2d 998, 51 C.C.P.A. 845, 139 U.S.P.Q. 496 (1963). A consideration of the board's decision as well as the appellants' and solicitor's arguments leads us to the conclusion that the correct statutory standard, i. e., nonobviousness, has been in contest throughout, even though the nomenclature has been imprecise.

The record presents three different methods of assessing data for the existence of unobvious results when combination herbicides are claimed.

The first test, embraced by the examiner and discarded by the board, is based on our *56 decision in In re Lemin, 408 F.2d 1045, 56 C.C.P.A. 1050, 161 U.S.P.Q. 288 (1969). Our opinion is said to require testing that compares the effectiveness of a claimed mixture of, e. g., 1 pound of A and 1 pound of B per acre, with that of 2 pounds of A per acre as well as 2 pounds of B per acre. It is said that if the effectiveness of the claimed mixture is greater than the total of the two single tests, then an unobvious result is demonstrated. The conclusion may well be correct, but a requirement that the claimed mixture be compared to an equal weight of its constituents is not to be found in Lemin.

Another manner of evaluating these data is disclosed by Poignant. This method compares the actual effectiveness of each of the components in the mixture at the amounts present in the mixture with the effectiveness of the mixture itself. For instance, if one pound per acre of herbicide A kills 50% Of the plants and half a pound of herbicide B kills 50% Of the plants, then, according to Poignant, if the effectiveness of the mixture is more than 75%, an unobvious result is shown. This test rests on the theory that if A kills 50% Then the best B can do is kill 50% Of the Remaining plants for an expected total of 75%.

The method applied by appellants and the board is similar to that utilized by Poignant, except that the effectiveness rates of the single herbicides are merely added. For the hypothetical situation outlined above, the expected effectiveness for the mixture would be 100%.

We evaluate the examples with the latter method simply because of the ostensible agreement between the board and appellants that it is appropriate. [FN7]

> FN7. As an aside, it seems that appellants have foregone an excellent chance to educate both the PTO and the court in their science. The record is not clear as regards the industrial standards and practices in evaluating data such as those presented in the specification. Although industrial standards are not necessarily determinative of what constitutes an unobvious result, they should go a long way in evincing what one having ordinary skill in the art looks at in making a choice between compositions. See In re Luvisi, 342 F.2d 102, 52 C.C.P.A. 1063, 144 U.S.P.Q. 646 (1965).

In any event, each of the entries in Tables I, II and III for compositions containing ethers I, II and III shows unobvious results under this test since the efficacy of the mixtures is, in each case, higher than the sum of the effectiveness of the constituent herbicides.

The next point at issue concerns the scope of proof offered in support of these claims.[FN8]

> FN8. The board also questioned the statistical significance of the proof. Admittedly, the number of plants used in the tests is not disclosed. Nevertheless, we see no reason to question the data on this basis without some indication either from the data or from the prior art that these types of tests give unreliable results.

Claims 6, 7 and 8 all require a FENAC/diphenyl ether ratio ranging between 1:1 and 4:1. Tables I, II and III (footnotes 3, 4 and 5, supra) provide data for a range of 1:1 to 2:1 for the composition of claim 6 (containing ether I) and a range of 2:1 to 4:1 for the compositions of claims 7 and 8 (containing ethers II and III respectively). The solicitor argues that the lack of data for the remainder of the claimed ranges mandates an affirmance of the board's decision.

[4][5] We feel that the unobviousness of a broader claimed range can, in certain instances, be proven by a narrower range of data. Often, one having ordinary skill in the art may be able to ascertain a trend in the exemplified data which would allow him to reasonably extend the probative value thereof. The proof, thus considered, might then be sufficient to rebut a PTO holding of prima facie obviousness.

The data pertinent to claims 7 and 8 appear to support such an extension, those to claim 6 do not appear to do so.

First, with regard to claims 7 and 8, consider in Tables I and II in the column marked 2 lb/acre of FENAC, the three entries for each of ethers II and III. These entries going down the table are equivalent to 16:1, 8:1 and 4:1 FENAC/diphenyl ether. The effectiveness Increases as it

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approaches the contested region of the *57 claimed range and yet still far outstrips the additive total of "expected" effectiveness. A similar conclusion may be drawn from the entries in the column drawn to 1 lb/acre of FENAC corresponding to ratios of 8:1, 4:1 and 2:1.

On the other hand, the data in Tables I and III corresponding to claim 6 (ether I) cover only a third of the range of claim 6 (1:1 to 2:1), and the effectiveness appears to decrease to the "expected" level as the untested region of that claimed range is approached. For instance, the entries at 1 pound/acre of ether I at both 1 and 2 pounds/acre of FENAC, (corresponding to 1:1 and 2:1 ratios, respectively) show the effectiveness to be only 30% And to approach the expected levels of 0% To 10%. Accordingly, the data do not support the breadth of claim 6.

In sum, we Affirm the board's decision with regard to claims 1, 3-6 and 9-15, and Reverse as to claims 7 and 8.

MODIFIED.

595 F.2d 48, 201 U.S.P.Q. 193

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